

ALLERGY

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To
DR. JOHN H. STOKES
Professor of Cutaneous Medicine
University of Pennsylvania School of Medicine
a scholar and true friend
this book is dedicated
with a deep sense of
admiration and gratitude

PREFACE TO THE SECOND EDITION

IN LESS than three years since its publication, the first edition of this volume has been exhausted. During this time, Portuguese and Spanish translations have appeared. We are indeed grateful for the manifest support and confidence of our colleagues and friends.

For many years, my collaborator, Dr. Philip M. Gottlieb, has helped in the preparation of this book and worked with me on numerous original papers. For that reason I have now adopted him as a permanent literary associate.

It is becoming increasingly apparent that the incidence of allergic diseases has attained an all-time peak. There are many instances in which the entire family, parents and children alike, suffer from some form of bronchial, nasal, gastro-intestinal, cutaneous, or cerebral hypersensitiveness, and very few in which at least one member is not afflicted. This state of affairs is truly alarming and calls for concerted action on the part of the medical profession. Now with the return of peace, a determined effort should be made by both National Allergy Societies to carry out and support basic scientific work designed to elucidate the fundamental causes of the hypersensitive state in man and animals. Special research institutes should be established in which biologists, chemists, physicists, immunologists, clinicians, and veterinarians may investigate the obscure causes which have made allergic diseases increase to such an extent that there is a very real danger that in the not too distant future every one of us will be allergic.

On the other hand, few branches of medicine have made such progress in the last three years as has allergy. This is best demonstrated by the immense literature which has appeared in that time, making it necessary to insert in the second edition nearly 1,300 new references and

to increase the reading matter by more than 10 per cent. Twenty-one new illustrations have been added.

In order to avoid bulkiness a double-column format was chosen. Moreover, small print was employed for technics, botanical discussions, case histories, and the like. A few hundred older references were omitted.

The following new sections were added: psychosomatic aspects of allergy; Rh factor, allergic bronchitis, allergic cough, and eosinophilic erythredema.

The following sections were materially enlarged: drug allergy, with particular attention to sulfonamides, penicillin, and thiouracil; endogenous allergy, toxic and allergic contact dermatitis, treatment of migraine; sensitivity to human plasma, the pathogenesis of lupus erythematosus, periarteritis nodosa, and rheumatic fever, the allergy of infectious diseases; the various test methods, the diagnosis and complications of asthma, and cellular passive transfer by means of the Urbach-Koenigstein method. No portion of the book has escaped revision. Finally, through the courtesy of Dr. M. B. Sulzberger, a complete list of the concentrations used in patch testing was appended.

Again we have not hesitated to give our opinions, interpretations, and ideas, particularly regarding treatment. However, as in the previous edition, an attempt has been made to present controversial subjects in an impartial manner.

Expenses incidental to the preparation of this book were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia, Pa.

The book is a genuine tribute to the generosity of the publisher, Mr. Henry M. Straton.

Philadelphia

ERICH URBACH

April 1946

PREFACE TO THE FIRST EDITION

THE vast importance of allergy in all aspects of medicine is reflected in the immensity of the literature, which has increased to such a point that no one person can hope to encompass all of it. There are, of course, some reference books covering the subject admirably, as well as a number of excellent special monographs that deal with their particular fields most thoroughly.

The study of allergy has made huge strides during the past ten years. Thanks to the close cooperation of immunologists, pathologists, internists, pediatricians, dermatologists, rhinologists, and ophthalmologists, new vistas of knowledge have been opened up and highly significant discoveries have been made, particularly as regards etiology, diagnosis, and the basic experimental background. The clinician must admit, however, that the allergic viewpoint in general and the allergic approach to treatment in particular still encounter rather considerable skepticism among the profession, and that, in fact, the available methods of prophylaxis and therapy of allergic diseases are, to a certain extent, inadequate. There are a number of reasons for this. The present generation of physicians—like the two preceding—was brought up in a medical era nurtured chiefly along chemical and bacteriologic lines. Therefore, their attention has been directed almost exclusively toward the discovery of the immediate causes of a given disease, while the predisposing factors, which often are as important as the eliciting agents, have been largely ignored. The argument might be advanced that, even when the predisposing conditions are recognized, it is frequently not possible adequately to deal with them, since this would involve fundamental alterations in the patient's mode of living, working, eating, and even thinking. But the great progress of the past few years inheres in the fact that we are no longer content merely to determine and eliminate the allergen, but also attempt to define the general influences responsible for the production and maintenance of the disease and to eliminate all such contributory elements. In other words, we

recognize that hyposensitization without elimination of the factors predisposing to allergy is, in most instances, only of temporary value.

Another reason why many therapeutic measures fail, is that they are usually predicated on the results of skin tests alone, and that the latter are more or less futile in certain conditions, particularly food, drug, and gastro-intestinal allergies. The emancipation of diagnosis from this one-sided approach, and the increasing emphasis on trial and exposure tests, such as environmental, elimination, nasal, and bronchial tests, are among the achievements of recent years.

We are beginning to understand that allergic diseases are by no means caused exclusively by exogenous agents. The writer has endeavored to show the significance of endogenous allergens—and most especially of the auto-endogenous agents—in the etiology of many conditions of hypersensitiveness, including some of hitherto unknown origin.

The intra- and subcutaneous methods of hyposensitization are quite ineffectual in food and drug allergies. In such cases measures of deallergization are helpful, especially those based on the principle of oral desensitization. The chief differences between hyposensitization and deallergization are given in some detail in the text, and their practical application is illustrated by numerous examples.

The concept of allergy is today commonly identified with that of hypersensitiveness; correspondingly, diseases of hypersensitiveness are generally called allergic diseases. This synonymy has, in the course of time, led to the designation of all kinds of clinical manifestations as "allergic," so long as they could be interpreted as the expression of an altered reactivity. Obviously such excessive broadening of the concept of allergy threatens to weaken it to the point of rendering it useless. The writer holds, therefore, that a given case may properly be called allergic only if the fact that it is mediated by an antigen-antibody reaction has been established in principle. If this cannot be demonstrated—or has not as yet been demonstrated—for the condition under

consideration, the term "pathergy" should be used to indicate that the disease is fundamentally one of hyper- or hyposensitivity.

As a science develops new terms must be coined to express new thoughts. Therefore the concepts "hetero allergy," "parallergy," and "metallergy" are discussed in some detail. Their value in our understanding of some phenomena of hyper- and hyposensitivity, as well as of the mechanisms underlying certain therapeutic methods including metal-
 lergic hyposensitization and deallergization is stressed. Similarly consideration is given the Schwartzman phenomenon from the standpoint of its significance as an important form of toxin hypersensitivity.

The goal that the writer has set for himself is to offer to the practitioner, to the specialist in all fields in which allergy plays a rôle, and to the student of allergy, a critical presentation, along with representative illustrations to serve as a guide in the diagnosis and management of the diseases of hypersensitivity. The scientific investigator will find a discussion of fundamental principles in the initial chapters of Part I, the rest of which is devoted to the methods of diagnosis and treatment. Part II

deals extensively with the more common etiologic agents while Part III comprises a discussion of the various diseases from the clinical and therapeutic viewpoints. The Appendix includes a series of detailed clinical record forms for the allergy patient as well as tables of concentrations for the substances used in patch testing.

In order to enable the reader to delve more deeply into problems of especial interest some 2300 references from the literature are presented in the form of footnotes. Every effort has been made to avoid duplication of the discussions in the text for the purpose of inclusiveness numerous cross references are supplied throughout.

The author has attempted to give an impartial presentation of the conflicting views on controversial questions, he has however, expressed his own opinions and critical comments wherever necessary. This, he felt, was not only the privilege but indeed the duty of a worker who, for almost twenty five years has intensively devoted himself to the subject both in the field of experimental investigation and in clinical experience with a large and varied material.

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The writer wishes to express his deep indebtedness to his associate, Dr Philip M. Gottlieb, for his indefatigable assistance in editorial matters, including verification of references, final revision of the manuscript, proof reading, and compilation of the indexes. Other invaluable contributions of his were the preparation of original pollination calendars, the provision of the botanic discussions of the plants that cause hay fever and the section on insects.

The writer also wishes to thank Drs K. Kornblum and L. Solis Cohen for the use of numerous roentgenograms, Dr H. Roessler for the electrocardiograms, Drs W. A. Feiler and R. F. E. Stier for numerous pictures of plants, Dr N. Schaffer for photomicrographs of pollen and molds, and Dr F. W. Wittich for photomicrographs of rusts and molds. To Mr H. J. Salomon, the author is thankful for expert editing of the manuscript.

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ERICH URBACH

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Part One

FUNDAMENTALS OF ALLERGY

CHAPTER I

HISTORICAL SURVEY

THE HISTORY of medicine shows that the prevalent political, social, and hygienic conditions characterizing various epochs, countries, and occupational groups are accompanied by certain distinctive types of disease. The medical historian of the future will undoubtedly have to report that the first half of the twentieth century was distinguished by an alarming increase in the incidence of allergic diseases in the so-called civilized countries.

Isolated cases of hypersensitiveness have, indeed, been mentioned throughout history. Lucretius (first century B.C.) is said to have coined the significant proverb, "One man's meat is another man's poison." Galen (A.D. 130-200) was aware of such a condition as allergy to goat's milk. And the Babylonian Talmud (second century) gives precise instructions on how to combat an intestinal egg hypersensitiveness by means of appropriate preparations of egg white (H. I. Goldstein). The physicians of the Middle Ages were well aware of the fact that some people became afflicted with severe attacks of sneezing or of asthma in the presence of certain flowers, shrubs, or trees (Botallus, 1565; van Helmont, 1600, Beningerus, 1673). Roses were specially suspect (Ledel, 1683, Hunerwolf, 1683; DeRebecque, 1691; Veit Riedlin, 1695). Timaeus (1667) and William Scott (1776) reported on violent *asthmatic paroxysms* produced by the effluvia of ipecacuanha; Willis (1621), on such attacks following consumption of certain foods.

The symptoms following transfusion with lamb's blood—described by Denis (1667)—were unquestionably manifestations of serum disease. Magendie (1839) observed that when dogs were given injections of foreign serum they acquired a strange condition often leading to death when a subsequent infusion was given

within ten to twelve days. This was probably the first instance of experimental anaphylaxis.

These few scattered and haphazard notes will at least serve to indicate that every case of hypersensitiveness was once such a rare occurrence as to merit special mention. That time has passed. At present the average practitioner is called upon almost every day to treat cases of allergy. The reasons for the almost universal allergization of the human race will be discussed elsewhere in some detail.

We shall first briefly consider the men whose names are outstanding in the science of allergy and whose basic investigations will frequently be referred to in this book.

We are indebted to C. Richet for the first fundamental contributions in this field. He undertook a series of systematic experiments (1898-1902) and succeeded in specifically sensitizing animals to a given poison (actinia toxin, eel serum) by means of a preliminary injection. This phenomenon he called "anaphylaxis"—i.e., removal of protection. The importance of Richet's work is in no way diminished by the fact that he assumed that the anaphylactogenic substance had to be primarily toxic. Arthus (1903) first recognized the fact that nontoxic agents, such as normal or foreign serum, could also elicit these manifestations of hypersensitiveness. And Arthus also demonstrated that repeated subcutaneous administration of serum will produce local reactions (Arthus phenomenon), sometimes so severe as to result in necrosis.

Theobald Smith is another pioneer in the field of experimental anaphylaxis. In addition to his other contributions, he discovered that guinea pigs are especially easy to sensitize. Then there are Rosenau and Anderson, Otto, Wolff-Eisner, and Besredka, who showed that

repeated injections of small doses of antigens in sensitized animals brought on a state of at least temporary insensitiveness. Besredka (1907) introduced the name "anti-anaphylaxis" for this procedure.

These and many other authors resorted to animal experimentation in their attempts to clarify the numerous problems arising in the study of the phenomena of hypersensitivity. However, it was von Pirquet (1903) who, on the basis of *clinical* observations and experiments on human beings, ingeniously promulgated the principles that have since become the basis of modern allergy. These studies were made on the theretofore almost unknown condition of serum sickness (on which he and Schick wrote the first detailed monograph) and on the clinical phenomena in vaccination and certain infectious diseases, including measles and tuberculosis. This great investigator advanced the theory that all disease symptoms that an organism acquires after acquaintance with any organic substance, living or nonviable, are attributable to an altered condition. He coined (1906) the term "allergy" (Greek *ἄλλη ἔργεια*, "altered capacity to react"). Von Pirquet also introduced (1910) the cutaneous tuberculin test (by means of scarification) and thus was the creator of modern skin testing in allergy. It might be of interest to mention here that some fifty years earlier, Blackley had described skin tests with pollen, this work, however, had fallen into oblivion.

In 1911, Noon and Freeman introduced the treatment of hay fever by means of intra cutaneous injections. R. A. Cooke, in the same year, performed the first recorded intra cutaneous tests for diagnostic purposes. During the next few years, Schloss, Walker, Coca, Cooke, and others made distinguished contributions toward the development of the technic of skin testing, and thus established this most essential diagnostic procedure.

The epicutaneous test, more commonly known as the patch test, so useful for the detection of allergic dermatitis, especially of occupational types, was described by J. Jadassohn as early as 1894. But this valuable technic did not become truly popular until it had been intensively employed by Bloch in Europe and Sulzberger in the United States.

The next great advance, important from

both the practical and the theoretic viewpoint, was made when Prausnitz and Kuestner (1921) first provided the method of passive transfer of hypersensitivity by means of blood serum. This technic now gave the clinician an opportunity to demonstrate the presence of antibodies as evidence of an allergic etiology in cases previously assumed to be so caused on purely clinical grounds. M. Walzer (1927) successfully employed this method in two other important problems: first, to identify the allergen by means of a passively prepared skin site in a recipient, when it is either dangerous or impossible in a given case to perform direct tests with the allergen; and, second, to show that all the mucous membranes of the human body can be allergized in the same way as the skin. In conjunction with Koenigstein Urbach (1924) developed a method of passive transfer for the demonstration of tissue antibodies, using the fluid from cutaneous blisters, either occurring naturally or deliberately raised with cantharides. Other technics that greatly advanced the experimental side of work on allergy are to be credited to Schultz and Dale (1912-1913) for the uterus test, and to Manwaring and Kusama (1917) for the lung perfusion test.

The study of allergy was immensely advanced by the brilliant work of Landsteiner (1927), who showed that a host of antigenic substances could become complete antigens by conjugation with proteins. The so called hapten theory first made it possible to consider several important forms of hypersensitivity—drug sensitivity, physical hypersensitivity, contact dermatitis—as being at least in part, manifestations of allergy.

The problem of the manner in which human allergization occurs was clarified by the fundamental work of many investigators, of whom only a few can be mentioned. Experimental sensitization of the skin by means of chemical substances was first achieved by Bloch, Sulzberger, and Landsteiner, that of the bronchial mucosa by means of inhalants by Ancona, van Leeuwen, and Busson, and that of the nasal mucosa by means of pollen, by Ulrich. Here we must also mention the work by Rosenau and Anderson, and Ratner on allergization of the fetus by the placental route.

We should now like to consider briefly the pioneer work done in relation to the various

allergic diseases. Meltzer (1910) first expressed the thought that asthma may belong to the group of anaphylactic diseases, on the basis of John Auer's demonstration that bronchospasm is an intrinsic feature of anaphylactic death in the guinea pig.

In the history of hay fever, the name of Bostock (1819) must be mentioned first. He wrote the earliest and now classic description. Elliotson (1839) adopted the lay term "hay fever" and held pollen largely responsible for the disease. But it was Blackley (1873) who, by means of brilliant experiments on himself (inhalation of dust from blossoms, and skin tests), first presented proof that hay fever is a pollen hypersensitiveness.

Duke (1925) in masterly fashion grouped all the hypersensitivities to cold, heat, pressure, and light under the heading of physical

allergies, and contributed important investigations in this field.

G. Schwartzman (1929) merits special mention as the author of the phenomenon that bears his name and that will probably play a major part in our understanding of certain forms of hypersensitiveness.

J. Jadassohn and Bloch in Europe, and notably Sulzberger and L. Schwartz in America made outstanding contributions to our knowledge of dermatitis as an allergic manifestation.

In conclusion, mention should be made of the names of Coca, Cooke, and Doerr as eminent scholars in expanding and clarifying the concept of allergy. We shall have frequent occasion to refer to their work. In addition, we should give credit to Moro (1926) for establishing the concept of parallergy, and to Roessle (1932) for that of pathergy.

CHAPTER II

THE PHENOMENA OF HYPER- AND HYPOSENSITIVENESS

ALMOST fifty years ago, von Behring introduced the terms *hypersensitiveness* and *hyposensitiveness* to refer to increased and decreased reactivity, respectively. Von Behring coined these words to designate the observation that, in the course of treatment with diphtheria or tetanus toxin an animal's state of reactivity frequently undergoes a considerable change. In this type of altered reactivity (known as toxin hypersensitiveness), the specifically hypersensitive animal will respond to an injection of toxin, not with anaphylactic manifestations but rather with disturbances dependent on the nature of the toxin. However, in comparing this toxin hypersensitiveness with *allergic* hypersensitiveness, in which the manifestations of the reaction do not depend upon the nature of the excitant allergen but entirely upon which organ is sensitized, it becomes apparent that the term hypersensitiveness is used for two entirely different types of reactivity.

This example will serve to emphasize the absolute necessity for establishing a single clear cut nomenclature in the study of immunology. The need for this is all the more urgent since numerous authors now employ such terms as hypersensitiveness, idiosyncrasy, atopy, anaphylaxis and allergy as nearly synonymous, while other authors use them in different and even opposite senses. This may ultimately lead to such confusion in the nomenclature that the basic concept would be endangered.

It appears therefore, that we must set up a clear and unequivocal system of nomenclature, based on demonstrated facts.

To begin with, we can no longer employ von Pirquet's concept of *allergy* in the widest sense of his original definition (1906). This embraced all alterations in the state of reactivity of an organism due to contact with any organic living or nonviable substance. However valuable and fruitful von Pirquet's contribution may have been, his term *allergy* must now be employed in a modified sense.

Under the leadership of Doerr¹, immunologists and allergists abroad united (1925) in recognizing as truly allergic only such reactions as are based on an antigen antibody reaction. Allergy was then defined as the alteration in the reactivity of an organism usually occurring after exposure to a substance, the antigen as the result of the production of specific antibodies the presence of these antibodies causes the organism to react to subsequent contact with the same antigen in a different manner than at the time of the first exposure—usually more rapidly and more intensely (Bloch²).

In Europe today, the viewpoint is generally accepted that an antigen antibody mechanism represents the basis of all allergic hyper or hyposensitiveness. In America however, opinion seems still to be divided. Certain eminent authorities here reject the postulate of an antigen antibody reaction on the following grounds: insistence on the demonstration of antibodies would necessarily exclude from the classification of allergy many well known and accepted conditions such as hypersensitiveness to drugs sensitization of the eczematous type (including even that deliberately produced with plant products and simple chemicals), and the phenomena of tuberculin and trichophyton allergy.

This group—led by Coca³ and Sulzberger⁴—employs the term *atopy* to designate those types of human hypersensitiveness in which an antigen antibody mechanism is demonstrable—a reaction based upon hereditary predisposition. These authors designate all other forms of human hypersensitiveness as *nonatopic allergy*. And anaphylaxis is the term they generally employ to denote a form of specific

¹ DOERR R. Arch v f Dermat u Syph 1:1 7 1926

² BLOCH B. Eighth Internat Cong Dermat & Syph Copenhagen 1930 p 93

³ COCA A F WALKER M and THOMMEN A A. Asthma and Hay Fever in Theory and Practice Springfield Ill Thomas 1931

⁴ SULZBERGER M B. Dermatologic Allergy Springfield Ill Thomas 1910

cally altered reactivity that can regularly be produced only in laboratory animals.

Others (including Zinsser, Kolmer, Topley and Wilson, Gay, Doerr, Rackemann, Vaughan, B. Ratner, Ramirez, and Urbach) do not favor this nomenclature. They point out that the results of recent experimentation in allergy and newer investigations into the chemoserology of antibodies have served to negate the premises that may originally have justified the concept of atopy. These authors insist, therefore, that differentiation between atopic and nonatopic allergy is no longer permissible (for a thorough discussion, see p. 9). Furthermore, it must be stated that almost all authors today agree that anaphylaxis is to be regarded as only a special type of allergic manifestation, not limited in its occurrence to animals.

It must be conceded, however, that not every phenomenon of hypersensitiveness is necessarily based on an antigen-antibody reaction; or, to put it more conservatively, the proof of such an antigen-antibody reaction is as yet frequently not available, since it is often impossible to demonstrate, chemically or biologically, the presence of secondary exogenous allergens (see p. 115). As pertinent examples we might mention the light dermatoses based on disturbed porphyrin metabolism, in which tolerance to light is re-established after pathologic intestinal flora is restored to normal (Urbach), or the cases of urticaria due to pressure, in which the eliciting factor, pressure, becomes ineffectual after the underlying intestinal disturbance has been cured (Urbach and Fasal). According to the definition of allergy above, these conditions are not allergic, yet they certainly represent reactions of specific hyperseositive-ness.

It is imperative to express all this clearly in the nomenclature.

A. THE CONCEPT OF PATHERGY

The necessity for an inclusive term for the various types of pathologic altered reactivities has led to several very interesting and valuable suggestions. The first of these was the creation of the concept *allergy*. "I suggest the term 'allergy' to designate this general concept of altered capacity to react," declared von

Pirquet.⁵ Even though this pioneer later set up certain postulates for the manner in which the alteration in reactivity takes place (recovery from a disease, previous exposure to bacterial or other substances foreign to the body, etc.), his definition still remains too vague. Coca, in 1931, suggested the comprehensive term *hypersensitiveness*. "Hypersensitiveness," Coca said, "should be defined as specific sensitiveness in man and lower animals that is mediated by a special mechanism." However, quite aside from the fact that von Behring had already made use of this term to designate the entirely different toxin hypersensitiveness, Coca's definition would seem to exclude (literally at least) the important states of hypo- and insensitive-ness. Stokes⁶ employed the phrase "broadening of the allergic state." Some French authors recommended the designation "intolerance", others suggested "hyperergy," "panallergy," and so forth. The writers feel that none of these terms is suited to serve as the general comprehensive designation for the various forms of pathologic altered reactivities.

In 1932, Roessle⁷ coined the term *pathergy* for the totality of the pathologic manifestations that can be elicited by a state of altered reactivity. Pathergies are not to be considered as the living organism's pathologically increased or decreased reaction capacities per se, but only as those manifestations that are based on an innate or acquired alteration in the organism's reactive capacity.

An example will make this clear. Everybody reacts with a certain amount of local erythema to a given pressure applied for a given length of time, however, if the subject reacts to the same pressure with marked redness and whealing, this represents an altered reactivity or pathergy.

For clinical purposes, the senior author⁸ in 1934 offered the following more sharply formulated definition: The concept of *pathergy* embraces all acquired and innate abnormally

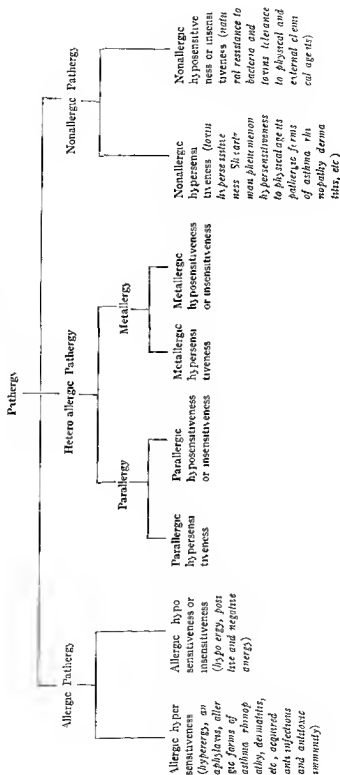
⁵PIRQUET, C. von. *München med. Wchnschr.*, 53: 1457, 1906.

⁶STOKES, J. H. *Fundamentals of Medical Dermatology*, revision 7. Philadelphia Univ. Press-Ylvanus, Dept. Dermat. & Ekt. Fund., 1942.

⁷ROESSLE, R. *Wien klin. Wchnschr.*, 45: 609, 1932, *Klin. Wchnschr.* 12, 574, 1933.

⁸URBACH, E. *Med. Klin.* 30: 80, 1934.

TABLE 1—Classification of the Phenomena of Hypersensitiveness



increased or decreased capacities of living tissues to react to the influence of chemical or physical agents, whether these agents have the character of antigens or not. Thus we may designate as a "pathergen" any substance that is capable of eliciting a pathergic reaction as defined, regardless of whether the reaction is based on an antigen-antibody reaction or is elicited in some other manner. The senior author further suggested³ using "pathergy" as the comprehensive term for all allergic and nonallergic processes of hyper- and hyposensitiveness, and subdividing pathergy into allergic, hetero-allergic, and non-allergic pathergies—of which, of course, only allergic pathergy corresponds to allergy in the strictest sense (i.e., hypersensitiveness based on an antigen-antibody reaction). Table 1 indicates the relationship of these forms of hypersensitiveness, which will be considered *seriatim* below.

We are well aware of the dangers inherent in any attempt at classifying all the manifestations of hypersensitiveness in tabulated form. Such a procedure might well create the impression that each group of phenomena represents a totally independent process that is entirely unrelated to any other process and that may therefore be considered as a strictly isolated entity. We wish to dispel any such impression at once. In fact, quite the contrary is true, for the suggested system of nomenclature and subdivision is so elastic that it readily admits of the correct classification of each phase of hypersensitiveness—for example, the transformation, often observed clinically, of an originally allergic hypersensitiveness into a state of polyvalent metallergic and finally nonallergic pathergy. On the other hand, a disease originally classified as belonging to the group of nonallergic pathergies will find its place in the group of allergic pathergies as soon as new methods of investigation reveal, in any given case, the existence of an antigen-antibody mechanism.

B. ALLERGY (ALLERGIC PATHERGY)

The establishment of the general concept of pathergy enables us to redefine more sharply the concept of allergy. Thus, allergy is to be considered as a condition appearing after previous—sometimes even *in utero*—

sensitization, based on an antigen-antibody reaction, and manifested as a hyper- or hyposensitiveness to a primarily nontoxic antigen (cf. definition, p. 4).

A great many pathologic states have been more or less arbitrarily designated as allergic. For more precise classification, Doerr³ has outlined four criteria which must be fulfilled before a condition may be properly accepted as being of truly allergic origin. These so-called four points of Doerr are:

(1) *Aberrance from the norm*, as evidenced by comparison between an individual's present and previous behavior, or, in a congenital case, between the given individual's behavior and that of others. For example, all members of a family eat strawberries and only one child suffers an attack of angioneurotic edema. When this occurs after the very first ingestion of strawberries, the reaction is described as one of innate allergy (though, as we shall note below, this conclusion is not absolutely justifiable; see p. 11). If the child has eaten strawberries several times previously, the reaction is one of acquired allergy.

(2) *Specificity*, either mono- or polyvalent. For example, when an individual is hypersensitive to only one agent, the condition is to be described as a monovalent specific allergy; when there is hypersensitiveness to all members of a given chemical group (e.g., all mercury preparations), the condition is called a group-specific allergy; when, on the other hand, the hypersensitiveness involves various but unrelated substances (e.g., neoarsphenamine and bismuth), it may be regarded as a polyvalent specific allergy. This condition is not to be confused with polyvalent metaspecific allergy (for examples, see p. 29) and polyvalent nonallergic pathergy. An illustration of the latter is seen when asthma attacks are elicited not only by dust, but by exhaust fumes from automobiles, by the odor of turpentine, etc.

(3) *Symptomatology of allergic reaction totally unrelated to the pharmacodynamic properties of the given allergen*. For example, in order to determine whether a contact dermatitis is of allergic or nonallergic nature, one must apply patch tests of the suspected chemical in concentrations that have proved in an

³ DOERR, R. Allergic Phenomena. In Handb. d. norm. u. path. Physiol. 13: 650, 1929.

adequate group of subjects not to be primarily irritating (toxic). The same is true in testing the reaction to a drug. If oral administration of atropine, for instance, elicits symptoms that are recognizable as essentially toxicologic, it is not an allergic reaction but rather a specific manifestation of a nonallergic hypersensitivity.

(4) *Proof of the organic basis of the allergic manifestation by demonstration of specific anti-substances (antibodies)*. This can be accomplished in any of several ways, namely by passive transfer of the reactivity by means of blood serum or of blister fluid (Prausnitz-Kuestner and Urbach-Koenigstein methods, respectively), by testing the reactivity of isolated organs or tissues by means of the Schultz-Dale experiment, by specific hypersensitization. As will be shown in some detail below, the demonstration of antibodies is by no means possible in every case. It will suffice, in principle, that the demonstration of the antigen-antibody mechanism can be made in a sufficient number of cases of a given type or during certain phases of these cases.

An allergen, then, is defined as a substance (or living organism or physical agent) that can be proved to be responsible for the production of antibodies within the body. Synonyms for allergen are antigen, anaphylactogen, idiosyncrasogen, and atopen. Antibodies are defined as specifically reacting substances of protein composition found in the serum or tissues of higher animals, produced in response to the introduction of allergens, and capable, on uniting with them, of reacting in some observable manner. Synonyms for antibodies include reagins, sensitizins, anaphylactins, agglutinins, precipitins, and antitoxins depending on the precise nature of the reaction in question.

Allergic pathergy is subdivided into allergic hypersensitivity and allergic hyposensitivity.

1 ALLERGIC HYPERSENSITIVENESS ✓

Untold numbers of laboratory experiments have established the fact that the phenomena designated as anaphylaxis and local anaphylaxis (Arthus phenomenon) fulfill all the

criteria of Doerr, given above. Generations of clinical observation, along with the demonstration of the presence of circulating or tissue antibodies, have shown that certain diseases in man are likewise examples of allergic hypersensitivity. Included in this category are all those diseases properly termed "allergic." Other less common conditions (hypersensitivity to physical agents, to drugs, and to bacteria or their products) may be allergic in nature, or may be the result of other types of pathergy. There is also convincing evidence that acquired anti-infectious immunity is merely a special type of allergic hypersensitivity. All this will be considered in detail in the second and third parts of this book. The basic principles and the nomenclature will be discussed herewith.

Allergy

Allergy is the term commonly used to denote all the protean manifestations of allergic hypersensitivity in man, as exemplified by those cases of asthma, pollinosis, urticaria, migraine, and the like, in which the four points of Doerr (p. 7) can be demonstrated.

Anaphylaxis

Richet suggested the term anaphylaxis to designate certain phenomena of hypersensitivity in experimental animals. These phenomena include constitutional reaction, (commonly known as anaphylactic shock) as well as severe local manifestations (known as the Arthus phenomenon). Detailed description and discussion of the significance of anaphylaxis follow in a separate chapter (p. 83). It will suffice here to say that the symptoms of anaphylaxis elicited experimentally in animals, and occasionally also observed in human beings, are characterized by their severity and acuteness. These symptoms represent an excessive reaction of defense, so violent that the consequences may be deleterious to part or to all of the organism. Richet thought at the time that this manner of reaction represented a state of defenselessness—a view that led to the choice of the designation anaphylaxis (i.e., "without protection").

Anaphylaxis should be considered as a special case of allergic hypersensitivity—a state that is brought about under certain

conditions, usually as the result of parenteral injection of a protein antigen—in animals and human beings.

A tendency persisted for some time, and especially abroad, to consider anaphylaxis as representing the very *prototype* of allergy. This erroneous impression was due to the fact that, long before human allergies were recognized, investigation of the problems of hypersensitiveness was carried out exclusively on animals. After the manifestations of hypersensitiveness in humans had obtained recognition, there was a general tendency to view all these manifestations with regard to their similarity to those achieved in animals. This attitude was of course erroneous, because the conditions employed in animal experiments are basically different from those under which allergization arises in human beings. In experimental animals the antigen is administered by injection repeated at will at intervals of only a few days, leading to rapid allergization; while in man the antigen usually reaches the tissues by bronchial, nasal, enteral, or epidermal absorption, leading to gradual allergization.

The unitarian school of thought among allergists, to which we subscribe, is of the opinion that allergic hypersensitiveness embraces all the phenomena that the school of dualists designate as atopic and, in the terminology of some, idiosyncratic. According to the former concept, anaphylaxis, as already mentioned, as well as acquired anti-infectious immunity, are simply special types of allergic hypersensitiveness. The conflicting viewpoints of the unitarian and dualistic schools may be presented as follows:

Atopy

"Atopy"¹ is a term coined by Coca² to differentiate certain forms of hypersensitiveness in man from anaphylaxis in experimental animals. The original definition has been expanded and enlarged, and the present understanding of the concept has probably been most clearly expressed by Feinberg³: "Atopy is a type of hypersensitiveness peculiar to man, subject to hereditary influence, presenting the

characteristic specific immediate whealing type of reaction, having the circulating antihody reagin, and manifesting certain peculiar clinical syndromes, such as asthma and hay fever." To these, Sulzberger then added neurodermatitis under the new designation of "atopic dermatitis."

One must grant Coca and Sulzberger that, at the time when the concept of atopy was formulated, clinical allergy and experimental anaphylaxis appeared to be separated by wide and irreconcilable differences. A few years of intensive experimental investigation, however, have sufficed to change the very basis of their assumption. Thus, leading immunologists (Zinsser, Enders, and Fothergill,⁴ Kolmer,⁵ Topley and Wilson,⁶ Gay,⁷ Bronfenbrenner,^{8,9} Seegal and Seegal,¹⁰ Doerr,¹¹ Kallós and Kallós-Defner¹²) and allergists (Rackemann,¹³ Vaughan¹⁴, Peshkin,¹⁵ Ratner and Gruhl,¹⁶ J. Jadassohn,¹⁷ Bloch,¹⁸ Urbach¹⁹) are now of the opinion that "anaphylaxis to proteins in animals and all the forms of human idiosyncrasy are basically related in mechanism, depending upon a cellular reaction between an antigen and a specific sessile antibody reagin which has been developed as a result of previous contact or sensitization" (Zinsser²⁰).

Can hypersensitiveness be divided into an anaphylactic and an atopic type? The answer to this question is of fundamental importance.

We shall, therefore, examine the reasons

¹ ZINSSER, H., ENDERS, J. F., and FOTHERGILL, L. R. D. *Immunology Principles and Application in Medicine and Public Health*. New York: Macmillan, 1939.

² KOLMER, J. A. *J. Lab. & Clin. Med.* 13: 905, 1928.

³ TOPLEY, W. W. C., and WILSON, G. S. *The Principles of Bacteriology and Immunology*. Baltimore: Wood, 1937.

⁴ GAY, F. P., et al. *Agents of Disease and Host Resistance*. Springfield, Ill.: Thomas, 1935.

⁵ BRONFENBRENNER, J. *Am. Rev. Tuberc.* 36: 293, 1937.

⁶ *Ibid.* *Tr. Am. Acad. Ophth.* 45: 30, 1941.

⁷ SEEGAL, D., and SEEGAL, B. C. in Gay¹¹.

⁸ DOERR, R. *Allergie und Anaphylaxie Handb. d. path. Mikrobiol.*, ed. J. I. (pt. 2) 239, 1929.

⁹ KALLÓS, P., and KALLÓS-DEFNER, L. *Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap.* 19: 173, 1937.

¹⁰ RACKEMANN, F. M. *Clinical Allergy*. New York: Macmillan, 1931.

¹¹ VAUGHAN, W. T. *Practice of Allergy*. St. Louis: Mosby, 1939.

¹² PESHKIN, M. M. *Discussion to Crep* ¹³.

¹³ RATNER, B., and GRUHL, H. L. *Proc. Soc. Exper. Biol. & Med.* 27: 514, 1930.

¹⁴ JADASSOHN, J. *Dermatologie*. Vienna: Weidmann, 1935.

¹⁵ URBACH, E. *Arch. Pediat.* 58: 482, 1941.

¹⁶ ZINSSER, H. *Resistance to Infectious Diseases*. New York: Macmillan, 1931.

¹ Greek *ἀτοπία*, "strange disease."

² FEINBERG, S. M.; *J.A.M.A.* 114: 2126, 1940.

that, at the time, caused Coca to segregate certain forms of human hypersensitiveness under the designation 'atopy'. This will be done in the light of more recent experimental and clinical observations. And we shall advance other evidence that leads us to believe in the basic identity of these two reactive mechanisms, making it necessary therefore for us to reject the concept expressed in the term atopy. The nine points advanced by Coca and his school in support of the theory of atopy are given below in italics, each being followed by a brief discussion of its present experimental status.

(1) *Experimental anaphylaxis may be induced at will in animal species with certain antigens. Atopic hypersensitiveness cannot be induced, even by artificial contact, in persons not subject to the atopic hereditary influence.*

The investigations mentioned below demonstrate that asthma and hay fever (the leading "atopic diseases") can be induced experimentally—not only in animals, but also under certain conditions in a high percentage of human beings not subject to hereditary influences.

Bussan and Ogata,²⁷ Sewall and Powell,²⁸ Ratner Jackson, and Gruhl,^{29,30} Alexander, Becke, and Holmes,³¹ Manteufel and Preuner,³² Kallos and Pagel,³³ Kallos and Kallos Deffer,³⁴ Prausnitz,³⁵ Courtwright and his associates,³⁶ and Urbach and his coworkers³⁷ have all succeeded in allergizing guinea pigs solely by having them inhale a dry antigen such as horse dander, castor bean dust, anti sheep serum, cotton dust, ragweed pollen, or egg white, either in a dry form or in a liquid state. These exposures were carried out in a natural manner

in specially constructed chambers. Repeated inhalations of the homologous antigen caused the allergized animal to react with manifestations that clinically roentgenologically histologically in the pharmacologic response to epinephrine and even immunologically (immunity after repeated inhalation³⁸) simulate human bronchial asthma in all respects (Kallos and Kallos Deffer³⁹).

Ulrich³⁹ allergized guinea pigs by insufflation of dry ragweed pollen into their nostrils. He found that repeated contact almost invariably resulted in local nasal reactions resembling hay fever.

Experimental production of asthma in human beings would be unethical and has therefore never been attempted. However we may mention here the unintentional experimental induction of asthma in man. In the course of an experimental investigation of diphtheria immunization, Bousfield and King Brown⁴⁰ exposed normal adults to finely atomized for mol toxoid in a closed room for fifty minutes. These individuals were exposed twice, with an interval of two weeks. Reactions following the first inhalation were negligible, but after the second they were rather severe in most instances (cough, tightness of chest). The dangers of the use of aerosols of similar nature in the prevention and treatment of influenza have been emphasized.⁴¹ Hopps and Moulton⁴² were able to produce serious allergic reactions and fatal anaphylactic shock in guinea pigs and rabbits by three to five exposures to finely atomized liquid antigens, such as various nonhomologous serums or egg albumen.

Furthermore, there are numerous clinical observations that definitely indicate that asthma can be achieved quasi experimentally in human beings, under given conditions. Thus, Ancona⁴³ reported the sudden appearance of asthma in 21 inhabitants of an Italian village. All these individuals had been at work in a mill, handling grain that had become infested by the mite *Pediculoides*

²⁷ BUSSAN B and OGATA N. Wien klin Wchnschr 37 870 1924

²⁸ SEWALL H and POWELL C. J Exper Med 24 69 1916

²⁹ RATNER B JACKSON H C and GRUEHL H L. Proc Soc Exper Biol & Med 23 17 1925

³⁰ Idem Am J Dis Child 34 23 1927

³¹ ALEXANDER H L BECKE W G and HOLMES J A. J Immunol 11 175 1926

³² MANTEUFEL P and PREUNER R. Ztschr f Immunstaetsforsch u exper Therap 80 65 1933

³³ KALLÓS P and PAGEL W. Acta med Scand nav 91 292 1937

³⁴ KALLÓS P and KALLÓS DEFFNER L. Schweiz Ztschr f Path u Bact 5 97 1942

³⁵ PRAUSNITZ C. Med Research Council SD Rep ser no 212. London His Majesty's Stat Off 1936

³⁶ COURTRIGHT L J HURWITZ S R and COURTRIGHT A B. J Allergy 13 271 1942

³⁷ URBACH E JAGGARD G and CRISMAN D W. Ann Allergy (in press)

³⁸ RATNER B and GRUEHL H L. Am J Hyg 10 236 1929

³⁹ ULRICH H L. J Immunol 3 433 1918

⁴⁰ BOUSFIELD G and KING BROWN W W. Lancet 1 491 1938

⁴¹ Ed formal JAMA 123 1631 1943

⁴² HOPPS H C and MOULTON S. Proc Soc Exper Biol & Med 51 244 1943

⁴³ ANCONA G. Policl u co (sez med) 30 45 1923

ventricosus. Van Leeuwen⁴⁴ was able to confirm these findings, clinically and in animal experiments.

Another striking example of a high incidence of induced asthma is that of so-called "ursol asthma," which occurs in 10 per cent of all employes in the leather-dyeing industry using that dye (Curschmann⁴⁵). Furthermore, Figley and Elrod⁴⁶ observed that individuals living in the vicinity of castor oil factories acquired asthma from the inhalation of castor bean dust. Towey, Sweany, and Huron⁴⁷ reported that 33 per cent of their patients exposed to moldy maple bark developed acute asthmatic symptoms. Similar reports of asthma following exposure under given conditions come from the flax industry and cotton-spinning mills in England. Numerous cases were observed when the materials used in manufacture contained strongly allergenic substances.

(2) *Experimental anaphylaxis follows a previous, intentional exposure to a given antigen* Human "atopies," on the other hand, often seem to occur without any demonstrable previous exposure to incitant substances

First of all, anaphylactic manifestations appear even in animals without any demonstrable sensitization. Thus, Sobernheim⁴⁸ performing serum injections on thousands of cattle, found that some of the animals reacted to the first injection with definitely pathologic manifestations identical with the immediate reaction shown by most of the cattle on their second serum injection. The non-experimental occurrence of anaphylactization in animals has been observed by Brunner, Altman and Bowman.⁴⁹ In dogs with naturally acquired active or past ascaris infestation, constitutional reactions were precipitated by intracutaneous tests with ascaris extracts.

Concerning human beings, it must be strongly emphasized that a negative history as regards exposure proves nothing. We now

know that allergization is very often brought about by way of the nasal, bronchial, intestinal, placental, and epidermal routes. It is therefore not at all surprising that sensitization can take place totally without the patient's knowledge. Furthermore, it must be borne in mind that the incitant substances are by no means always exogenous antigens. We have good reason to assume that endogenous allergens (i.e., substances produced within the body and capable of assuming the character of antigens under given conditions) merit at least as much consideration as do the exogenous ones. Another important possibility involves the action of partial antigens, or haptens. A few examples will serve as illustrations.

There are patients who react to what is unquestionably their first injection of horse serum with severe immediate manifestations—cases in which no previous contact with horse serum can be proved. According to De Besche,⁵⁰ Ratner,⁵¹ Sumner, and Kopaczewski, however, these apparently inexplicable reactions may very well be due to previous contacts with horse dander (inhaled) or horse meat (ingested). The investigations of Rackemann and Simon,⁵² as well as those of Grow and Herman,⁵³ reveal a very high incidence of latent allergy to horse dander among the general population. Among individuals in constant contact with horses, Salén and Juhlin-Danafelt⁵⁴ found a high percentage of hypersensitiveness to horse dander.

Balgeat, Moro, Gyorgy, and many other have reported the following observation. Cases of infantile dermatitis showed a definite aggravation of the skin condition when the patients, till then breast-fed, were changed to a diet of cow's milk and egg white. György⁵⁵ was able to demonstrate that this allergization to cow's milk and/or to egg is attributable to traces of these substances contained in the mother's milk, and thus previously ingested by the infant. He showed that these allergic nursing infants gave positive skin reactions when the mother (nonallergic) had partaken of

⁴⁴ LEEUWEN, W. S. VAN, BIEU, Z., and VAREKAMP, H. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 40: 552, 1924.

⁴⁵ CURSCHMANN, H. *Muenchen med. Wchnschr.* 68: 195, 1921.

⁴⁶ FIGLEY, K. D., and ELROD, R. H. *JAMA* 99: 79, 1928.

⁴⁷ TOWEY, J. W., SWEANY, H. C., and HURON, W. H. *JAMA* 99: 451, 1932.

⁴⁸ SOBERNHEIM, G. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 5: 619, 1919.

⁴⁹ BRUNNER, M., ALTMAN, I., and BOWMAN, E. *J. Allergy* 15: 2, 1944.

⁵⁰ BESCHE, A. DE. *J. Infect. Dis.* 22: 594, 1918.

⁵¹ RATNER, B. *JAMA* 94: 2046, 1930.

⁵² RACKEMANN, F. M., and SIMON, F. A. *J. Allergy* 6: 184, 1933.

⁵³ GROW, M. H., and HERMAN, N. B. *J. Allergy* 7: 128, 1935.

⁵⁴ SALÉN, E. B., and JUHLIN-DANAFELT, J. *Acta med. Scandinav.* 84: 505, 1935.

⁵⁵ GYÖRGY, F. *Handb. d. Kinderh.* 10: 45, 1935.

egg or of cow's milk, and that the skin reactions became negative when the mother or wetnurse eliminated cow's milk or eggs from her diet. Other instances of the transfer of antigens to the nursing by way of mother's milk are given below (p 47). These experiments certainly speak for unrecognized allergization by way of the enteral route.

Mere mention will be made here of transplacental allergization as demonstrated by the well known experimental work of Ratner (see p 48).

Concerning bronchial allergization, see the discussion under (1) above.

The extensive work of Landsteiner, Sulzberger, Haxthausen, and others has confirmed the fact that contact dermatitis is based on epidermal allergization.

In addition to allergization resulting from such mechanisms produced by exogenous agents, and occurring almost always without the patient's knowledge, there are also those forms of allergization originating entirely within the body. These inevitably are bound to arise without the individuals being at all aware of them—as, for example, bacterial allergization initiating from a focus of infection. An ingenious experiment illustrates the probable mechanism of such a process. Burky⁶⁶ sensitized rabbits with a ragweed toxin mixture, obtained by letting toxin producing staphylococcus grow in a culture medium containing ragweed protein. After receiving injections of this mixture, rabbits responded to inhalation of ragweed pollen with anaphylactic reactions. Hecht, Sulzberger, and Weil⁶⁷ similarly employed the synergistic action of Staphylococcus toxoid in sensitizing rabbits to homologous skin. Hopkins and Burky⁶⁸ have presented evidence that certain dermatoses of unknown cause in human beings may be due to local sensitization to epidermal keratin or a product of keratin, after it has combined with Staphylococcus toxin liberated in the skin by the growth of a low grade toxin producing organism. Furthermore, there are fairly numerous clinical examples of auto-

allergization to hormonal substances as well as to substances that have become foreign to the organism (e.g. altered tissue protein). In short there can be allergization to endogenous allergens.

We must also remember that all these forms and types of allergization when employed in animal experiments produce allergic manifestations that usually present the same clinical picture as seen in man (asthma, rhinopathy, contact dermatitis, etc.). In consequence it appears safe to assume that human allergization depends almost invariably upon previous exposure to the incitant substances.

(3) *The substances that incite human allergies (atopies) are often nonantigenic in the sense that they are incapable of inciting antibody production or of sensitizing animals.*

Numerous experimental studies have served to invalidate this conclusion. We now know that guinea pigs and other animals can be actively allergized to pollen in a great many ways. The same is true of sensitization of animals to horse dander, house dust and similar allergens. Other substances—i.e. those of nonprotein nature (haptens)—cannot of course, sensitize directly, but must first be completed by combining with a protein substance (the "carrier") to form conjugate protein antigens (Landsteiner, Sulzberger).

(4) *Animals can readily be sensitized experimentally. In human beings, on the other hand, it is difficult—almost impossible—to achieve intentional sensitization.*

If it were permissible to experiment on human beings in the same manner as we do on animals, we should unquestionably elicit similar anaphylactic manifestations. This statement is based on reported experiences with patients who, while under anti-allergic treatment with pollens, peptone, milk, horse serum and other preparations displayed anaphylactic shock of the greatest severity. Furthermore it is well known that anthelmintics, grain mites, nickel, ursoil, and other substances quite frequently elicit allergic manifestations in individuals coming into frequent contact with them.

Recent investigations—notably by Landsteiner, Sulzberger, Nathan, Haxthausen, and others—have shown that by applying the

⁶⁶ BURKY E. L. J. Allergy 5: 466, 1934.

⁶⁷ HECHT R., SULZBERGER M. B. and WEIL H. J. Exper. Med. 78: 59, 1943.

⁶⁸ HOPKINS H. H. and BURKY E. L. Arch. Dermat. & Syph. 49: 124, 1944.

principles of baptenization, human and animal skin and mucous membranes can be similarly allergized to numerous chemicals and medications. According to Landsteiner and Jacobs,⁵⁹ the same happen that elicits contact dermatitis in sensitized animals when applied to the skin, will cause anaphylactic death when injected intravenously. Thus, once again, it would appear that the contention that human beings cannot be intentionally sensitized is based solely on differences in the experimental conditions to which animals and human beings are subjected.

(5) *Experimental anaphylaxis is based on an antigen-antibody mechanism and is characterized by the presence of anaphylactic antibodies. These antibodies are demonstrable by passive transfer of the anaphylaxis to other animals. In human allergies, on the other hand, only antibodies named "reagins" by Coca are demonstrable; and these can be transferred only from man to man by the Prausnitz-Kuestner technique (and are therefore often called Prausnitz-Kuestner antibodies). Furthermore, the blood of anaphylactic animals contains precipitins, which are not found in allergic patients.*

The claim has been made that, in order to identify human with animal hypersensitivity, it would be necessary to demonstrate in the blood of the allergic patient an "anaphylactic antibody" capable of passively sensitizing guinea pigs. This claim must be rejected for two reasons: (1) according to our present knowledge, the presence of humoral antibodies is not a necessary criterion of allergy, because allergy depends primarily on the presence of tissue antibodies; (2) it is known that guinea pigs, for example, cannot be passively rendered anaphylactic by humoral antibodies produced by experimental allergization of rabbits, rats, chickens, horses, and other animals with protein antigens. Thus, Avery and Tillet and Gerlach have been unsuccessful in passively transferring anaphylaxis to guinea pigs with horse serum. Even the passive transfer of anaphylaxis to a normal guinea pig with the serum of a hypersensitive guinea pig may fail in the absence of a sufficiently high precipitin titer.

However, we shall not base our contention

on these facts alone. There is further proof, based on experimental studies, to show that anaphylactic antibodies and the so-called atopic reagins are very closely related and perhaps even identical.

De Besche⁶⁰ has presented evidence that the human skin can be sensitized by the serum of rabbits hypersensitive to horse protein. Ratner and Gruel⁶¹ have performed similar experimental transfer to man, using the serum of guinea pigs sensitized to alum-precipitated ragweed extract. Winkenwerder, Eagle and Arhesman,⁶² also Sherman, Stull, and Hampton,⁶³ have reported transfer of sensitivity to human skin by means of serum from guinea pigs previously sensitized to pollen extract. Brunner, Altman, and Bowman⁶⁴ were likewise successful in passively sensitizing human skin sites to ascaris by the use of serum from dogs with previous nematode infestations, as well as that from a dog actively sensitized with pig-ascaris extract. Precipitins were absent from the dogs' serum and the skin-sensitizing antibodies were, like "atopic reagins," heat labile.

On the other hand, there are several convincing reports that humoral antibodies of allergic human beings are capable of transferring sensitivity to animal species. Thus, Caulfield and his co-workers⁶⁵ reported the successful sensitization of *Macacus rhesus* monkeys, using the serum of a human case of ragweed hay fever. Employing human serums containing antibodies to peanut, cottonseed, flounder, poison ivy, and horse serum, passive local cutaneous sensitization of rhesus monkeys was also demonstrated by Straus.⁶⁴ Ratner and Gruel⁶¹ report anaphylactization of a guinea pig with the serum of a human being allergic to horse dander.

The success of numerous experimental transfers—in both directions—answers the question as to whether "atopic reagins" can be produced by experimental animals. In showing that the antibodies associated with human

⁵⁹ BESCHE, A. DE. *Acta path et microbiol Scandinav* 6: 113, 1929

⁶⁰ WINKENWERDER, W. L., EAGLE, H., and ARHESMAN, C. E. *J Immunol* 36: 435, 1939

⁶¹ SHERMAN, W. B., STULL, A., and HAMPTON, S. F. *ibid* 36: 447, 1939

⁶² CAULFIELD, A. H. W., BROWN, M. H., and WATERS, E. T. *J Lab & Clin Med* 22: 657, 1937

⁶³ STRAUS, H. W. *J Immunol* 32: 251, 1937

⁵⁹ LANDSTEINER, K., and JACOBS, J. *J. Exper Med* 61: 625, 1936.

hypersensitiveness (the so called reagins) can be transferred from man to animal—just as the hypersensitiveness induced in an animal can be transferred to the human skin—we remove one of the chief obstacles to the complete identification of experimental anaphylaxis with clinical allergy or atopy.

Further evidence along the same lines is found in the reports of Weil and Reddin⁶⁶ and Reddin⁶⁸ that 'atopic sensitivity' to ragweed pollen arising spontaneously was discovered in 40 per cent of a herd of cattle. Not only was cutaneous hypersensitiveness to ragweed pollen antigen present, but there was demonstrated in the serum of these animals antibodies which were thermolabile, neutralizable by the specific antigen, and capable of passively transferring the hypersensitiveness to nonsensitive cattle. Moreover, both thermolabile and thermostable antibodies were identified, such as exist in human beings (Loveless). It appears therefore, that all the immunologic mechanisms that have been found in human beings can also be demonstrated in cattle. The similarity of these findings to those in human allergy presents, in our opinion, another point destroying the barrier between allergy and atopy.

Coca points out that in experimental anaphylaxis, precipitins are regularly encountered while in human allergies they are scarcely ever demonstrable. Despite the fact that definite proof has not yet been advanced to show that precipitins and antibodies are identical, it is now generally accepted that the demonstration of antibodies and precipitins in the blood is much less important than demonstration of their presence in the tissues. This assumption is based on the evidence that both experimental anaphylaxis and human allergy are cellular reactions; therefore the presence of tissue antibodies is obviously of much greater significance than the presence of antibodies in the blood serum. Matsumoto has, in fact, demonstrated precipitins in the organs and tissues of guinea pigs long after they had disappeared from the blood. Seegal and Seegal¹ found typhoid agglutinin present in the tissues in a concentration from two to four times that in the blood. Occasionally, they

were able to demonstrate agglutinins in the tissues even when none at all could be found in the blood. It should also be recalled that Landsteiner demonstrated the presence of precipitins in both human beings and animals experimentally sensitized to simple chemical substances.

(6) *Human allergy (atopy) is a hereditary manifestation in accordance with the medelian formula. Experimental anaphylaxis on the other hand can be transmitted only passively, and then only in the first generation.*

A wealth of examples refutes the claim that asthma and hay fever—the chief representatives of human allergy (atopy)—are mainly attributable to hereditary influence. If it were really true that the hereditary factor is of such great importance, how should we explain the fact that within one generation (1900-1930) the number of cases of these diseases in America alone, rose from a few tens of thousands to a figure of several millions? The importance of exposure to allergens—rather than of the hereditary factor—is shown in a most enlightening study by Clarke and Leopold.⁶⁷ These authors compared two groups of hay fever patients with regard to ragweed allergy. One group consisted of persons born in America—the other of persons born in Europe (where ragweed is practically unknown). The European born patients were found to acquire ragweed hay fever later in life, but to require the same average incubation period⁶⁸ after their first contact with ragweed pollen, regardless of their age at the time of first exposure.

The studies of Hara⁶⁹ also speak against the significance of the hereditary factor. Hay fever is practically unknown in Japan, but about 35 per cent of the Japanese population of southern California are afflicted with the disease. After coming from Japan to California, it takes these Japanese born individuals between five and fifteen years to acquire hay fever. Hara attributes these facts to the meteorologic and botanic conditions in Japan. Among his cases of asthma—representing largely Japanese peasant stock—Matsumoto⁶⁹ found that only 3 of 115

⁶⁷ CLARKE J. A. JR. and LEOPOLD H. C. J. Allergy 11: 494 1940

⁶⁸ HARA H. J. Arch. Otolaryng. 30: 323 1939

⁶⁹ MATSUMOTO S. Otologia (Fukuoka) 9: 100 1932

⁶⁶ WEIL A. J. and REDDIN L. JR. ibid 47: 345 1943

⁶⁸ REDDIN L. JR. Am. J. Vet. Research 6: 60 1945



FIG 1 Characteristic movement of dog during ragweed pollination season. Same response was elicited by ophthalmic test with ragweed pollen out of season (Courtesy Dr F W Wittich and *Journal of Allergy*)



NATURALLY OCCURRING HAY FEVER IN DOG

FIG 2 Characteristic movement of dog during ragweed pollination season

Same response was elicited by nasal test with ragweed pollen out of season (Courtesy Dr F W. Wittich and *Journal of Allergy*)

patients (26 per cent) were subject to hereditary influences

Dahlberg,⁷⁰ in an exhaustive study, has discussed the question of the heredity of predisposition to allergy. He concluded that present knowledge and particularly the experimental evidence does not grant heredity the important rôle usually assumed.

Moreover, we may again call attention to the successful experimental production of asthma in animals and human beings by the bronchial route, and to the fact that allergy can even develop spontaneously in lower animals. This last link in a convincing chain of evidence was established by Wittich.⁷¹ He reported a dog that has manifested typical hay fever symptoms in the fall season for six years past. This was established by ophthalmic (FIG. 1), nasal (FIG. 2), and skin tests, and passive transfer (FIG 3), as well as by successful hyposensitization. Analogous instances have been described by Thomas⁷² and Ruiz Moreno and Bentolila.⁷³ The former observed a dog with repeated attacks of seasonal bronchial asthma due to ragweed pollen and relieved by ephedrine. The same animal had seasonal



FIG 3 RESULTS OF PASSIVE TRANSFER TESTS WITH SERUM OF DOG EXHIBITING HAY FEVER SYMPTOMS

Recipient was dog of different species 1 = ragweed 2 = Russian thistle 3 = short ragweed 4 = prairie sage 5 = giant ragweed 6 = control (Courtesy Dr F W Wittich and *Journal of Allergy*)

hay fever with nasal itching and watery rhinorrhea, and, in the winter, asthmatic

⁷⁰ DAHLBERG, G. in KALLÖS, P. (ed.) *Fortschritte der Allergie* Lehre, New York Karger, 1939

⁷¹ WITTICH, F W. *J Allergy* 12, 245, 1941

⁷² THOMAS, J W. *Ann Allergy* 1: 163, 1943

⁷³ RUIZ MORENO, G., and BENTOLILA, L. *ibid* 3: 61, 1945

bronchitis following acute respiratory infection. In the latter's case, a 3 year old dog with perennial rhinopathy characterized by sneezing and watery nasal discharge along with crusted eczematous skin lesions, positive cutaneous reactions were obtained with dust, corn, oats, and cacao. The condition was controlled by elimination diet but recurred when the responsible foods were again given. Passive transfer to another dog was successful. A generalized reaction with pruritus, reaction of the dermatitic lesions, tachycardia, tachypnea and dyspnea occurred following the skin tests, and could be controlled by epinephrine. Precipitins were not found in the serum. Veterinarians state that hay fever like symptoms confined to the ragweed season are not too infrequently seen in dogs and cats.

The general failure to appreciate the existence of spontaneous hypersensitive states in animals stems from the fact that investigation of allergic diseases has been largely restricted to human medicine. The pathology of other mammals has been little investigated from the point of view of modern immunologic concepts. However, there are some observations of diseases in animals that can be definitely ascribed to allergy. In dogs, the food allergic origin of angioneurotic edema was ascertained by Phillips⁴ on the basis of feeding experiments and cutaneous tests. Schnelle⁵ and Wittich⁶ showed that some "eczemas" in dogs were due to food allergy, while allergic reactions in this animal were also described by Burns⁷ and Pomeroy.⁸ Vaughan⁹ mentioned a case of hypersensitivity to pine pollen in an Irish wolfhound similar to the case of Wittich mentioned above. Schroeder¹⁰ reported a baby walrus whose dermatitis was promptly cured when the milk on which it was fed was omitted. Bray¹¹ mentioned that hay fever was observed in England in a herd of pedigree cattle. Further examples were found in a report by Brownlee.¹² Serum sickness is known

in both horses and cattle (Gerlach¹³ Loustau and Rodriguez¹⁴). Such observations point to the existence of true allergy in these two species.

The way in which animals become sensitive to bacterial antigens like tuberculin and mallein, and the type of immediate response to bacterial products like *Brucella* polysaccharide (Libby and Joyner¹⁵), and the frequent response to anaphylactogens with asthma, diarrhea, and urticaria all suggest that mammals generally reveal the same gamut of responses to sensitizing stimuli as do human beings (Weil and Reddin¹⁶).

On the other hand in allergic contact dermatitis, which is definitely considered nonatopic by Coca and Sulzberger, Chase¹⁷ of Landsteiner's laboratory was able to establish strains of guinea pigs with significantly different susceptibilities toward a compound of simple structure, such as 2,4-dinitrochlorobenzene, as well as poison ivy. This is direct evidence that hypersensitivities of nonatopic character can be influenced by heredity.

All these facts make comprehensible Zinsser and Bayne Jones's¹⁸ conclusion. It is thus clear that, as far as heredity and preliminary sensitization are concerned, there need not be any sharp dividing line between the forms of hypersensitivity of man and those observed in animals.

(7) *An anti anaphylactic phase of variable duration always follows a nonfatal anaphylactic shock in guinea pigs such a phase is not observed in human beings*

This statement is incorrect, regarding both guinea pigs and man. For, when a human being responds with a severe anaphylactic shock (for example following injection of too large a dose of pollen extract) there can often be observed a subsequent anti anaphylaxis lasting days, weeks, and even months. In fact, this observation has induced certain authors to recommend desensitization by means of macroshocks (Kalk). Furthermore, the appearance of anti anaphylaxis in guinea

⁴ PHILLIPS J. McI. J. A. M. A. 78: 497, 1922.

⁵ SCHNELLE G. B. North Amer. Vet. 14: 37, 1933.

⁶ WITTICH F. W. Veterinary Section Annual Meeting of American College of Allergists, June 1934.

⁷ BURNS P. W. J. A. Vet. M. A. 83: 62, 1933.

⁸ POMEROY B. S. Cornell Vet. 24: 335, 1934.

⁹ SCHROEDER C. R. J. A. Vet. M. A. 83: 810, 1933.

¹⁰ BRAY G. W. Recent Advances in Allergy, ed. 2. Philadelphia: Blakiston, 1934.

¹¹ BROWNLEE A. J. Comp. Path. & Therap. 53: 55, 1940.

¹² GERLACH F. Ztschr. f. Immun.-forsch. u. exper. Therap. 34: 75, 1922.

¹³ LOUSTAU J. and RODRIGUEZ A. Re. de med. et 26: 462, 1940.

¹⁴ LIBBY R. L. and JOYNER A. L. J. Bact. 41: 0, 1941.

¹⁵ CHASE M. W. J. Exper. Med. 3: 11, 1941.

¹⁶ ZINSSER H. and BAYNE JONES S. A Textbook of Bacteriology, ed. 8. New York: Appleton-Century, 1939.

pigs is dependent upon the conditions of the experiment. Thus, Ratner,³⁶ as well as Kallós and Pagel,³⁷ reported that animals sensitized solely by inhalation do not as a rule show the state of anti-anaphylaxis that is observed in guinea pigs after repeated parenteral injections. This general absence of anti-anaphylaxis—especially in animals in which as many as twenty-eight successive attacks were induced by daily contact with the specific dust—is closely analogous to conditions in human beings.

(8) *In experimental anaphylaxis, desensitization can be achieved by suitable administration of the exciting agent. But in clinical allergy (atopy) such desensitization cannot be achieved.*

Topley and Wilson¹² correctly point out that the first part of this postulate is applicable to only a few animal species. For example, rabbits that have been sensitized to horse serum or to egg white cannot be desensitized. On the other hand, there have been quite a few observations of cases of asthma and hay fever that were successfully desensitized or deallergized by appropriate and repeated administration of the antigen. It must also be borne in mind that it is quite easy to desensitize specifically a locally sensitized area of human skin.

(9) *Those forms of human hypersensitivity that Coca has named "atopic" are characterized by a specific immediate whealing type of skin reaction, while bacterial hypersensitivity is characterized by a late reaction of the "tuberculin type."*

This differentiation was subsequently withdrawn in the following words: "Positive wheal reactions are found in cases of human hypersensitivity not of familial occurrence and without the characteristics of the so-called atopic group" (Sulzberger). Moreover, a number of reports attest to the occurrence of the specific immediate whealing type of skin reaction in animals, both experimentally sensitized and with naturally acquired allergic states.

These experimental and clinical observations have invalidated the grounds that, at the time, moved Coca to differentiate fundamentally between certain forms of human

hypersensitivity and experimental anaphylaxis. This is not to say that certain manifestations of hypersensitivity (e.g., asthma, hay fever, neurodermatitis) are not peculiar to human allergy. But, as we have shown, this depends less on basic differences than on certain extrinsic factors; for, when the same conditions of allergization are imitated, the same clinical picture can be produced in the experimental animal. (Neurodermatitis probably represents an exception, since it has not as yet been reproduced in animals.)

It seems that Coca's disciples are now aware of the difficulty of attempting to adhere logically to the principles of atopy. Thus, Simon³⁷ points out that poison ivy dermatitis—which can be produced in monkeys, guinea pigs, and human beings—properly belongs in the category of experimental anaphylaxis. On the other hand, the extreme degree of hypersensitivity to poison ivy often seen clinically probably cannot be reproduced at will, and should hence be placed in the atopic group (Simon). No better example could be found to illustrate the weakness of the concept of atopy. Likewise, most cases of human hypersensitivity to horse serum are relatively slight, can be reproduced at will, and occur in all or nearly all injected individuals. This is the reason why Coca refuses to consider serum sickness as an atopic manifestation, although it is always possible to demonstrate the presence of Prausnitz-Kuestner antibodies as evidence of antibody production against such a typical atopen as horse serum (Tuft and Ramsdell³⁸). But the rare cases of severe human hypersensitivity to horse serum are included in the atopic group. Cooke³⁹ brands the term "atopic dermatitis" as unfortunate, "for the word atopy is used by some to emphasize the hereditary feature; by others to indicate the existence of and the etiologic significance of the wheal-reacting type of allergy; and by many interchangeably as though the two were synonymous."

It is evident that just as soon as any difficulties appear, all logical pursuit of the principles seems to be abandoned. Thus, Sulzberger⁴ states: "Neither reactions on skin test

³⁶ RATNER, F. A. *Ann Int Med* 12: 178, 1938.

³⁷ TUFT, L., and RAMSDELL, S. G. *J Immunol* 16: 411, 1929.

³⁸ COOKE, R. A. *J Allergy* 15: 203, 1944.

³⁹ RATNER, B. *Am. J. Dis Child* 58: 699, 1939.

nor Prausnitz Kuestner antibodies are the actual determinants of atopic disease. For as we have seen both of these allergic alterations may be found without accompanying clinical disease and on the other hand both may be absent in the presence of clearly atopic clinical conditions. What then is left? The disposition to certain particular allergic diseases? We shall not deny that there does exist a certain hereditary predisposition in regard to asthma and neurodermatitis but this hereditary factor merits consideration as only *one* of the factors predisposing to allergy.

On the other hand the similarities between human allergies and animal anaphylaxis are so fundamental that all these forms of hyper and hyposensitiveness must be regarded as varying clinical expressions of one basic underlying mechanism—viz a cellular antigen antibody reaction. For all these many reasons it is apparent that the term atopy should be abandoned as quickly as possible.

Idiosyncrasy

The supporters of the theory of an independent idiosyncratic type of reaction advance several arguments notably the following: (1) There are states of hypersensitiveness that are apparently not acquired but innate because manifestations appear on the very first contact with the allergen. (2) These states are observed only in a relatively small number of human beings. (3) They are never observed in animals.

All these arguments can now be definitely refuted. One can never state with absolute certainty in any case that any particular contact with a given antigen really represents the very first contact with this antigen. The work of Ratner especially has convincingly demonstrated that a fetus can be allergized *in utero* and that a nursing infant can be sensitized by way of the mother's milk. The once broad gap dividing the apparently constitutional idiosyncrasies from acquired allergies has been totally eliminated by experiments that achieved deliberate allergization of 100 per cent of the human and animal subjects (Bloch, Landsteiner, Sulzberger, etc. see p. 44). For these reasons we join Kolmer, van Leeuwen, Frei and numerous other authors in demanding either that the designation

idiosyncrasy be dropped entirely or if the word has become too deeply rooted in the language that the term be employed synonymously with allergic hypersensitiveness.

Immunity

As outlined above anaphylaxis is but one particular type of allergic hypersensitiveness (allergy) while atopy and idiosyncrasy are conditions which according to present knowledge are identical with allergy proper. On the other hand immunity is also a form of hypersensitiveness but a special form which deserves separate study and analysis.

Before a discussion of the mechanism of immunity the apparent paradox of including acquired anti-infectious and acquired anti-toxic immunity in the category of allergic hypersensitiveness should be explained. At first glance one would be inclined rather to consider these phenomena as expressions of hypo or even insensitiveness since immunity connotes a state of protection while hypersensitiveness is often erroneously thought to be a state of defenselessness. However a review of the experimental and immunologic evidence (Urbach and Gottlieb⁹⁰) shows that acquired immunity may well be regarded as a special type of allergic hypersensitiveness. It must be granted though that there is another view, namely that immunity and allergy are independent and unrelated processes. This concept championed by Rich⁹¹ has gained a considerable following.

The whole question is not one of merely theoretic significance. If it were possible for example to abolish tuberculin hypersensitiveness at the same time leaving the mechanism of immunity intact the liability to an extensive necrotic and caseous form of tuberculosis would be greatly reduced. Moreover an understanding of the nature and extent of the hypersensitive reactions produced in the sensitized body by small numbers of bacteria or minute amounts of their proteins is essential in the interpretation of the lesions and symptoms of infectious diseases.

For the sake of clarity it is advisable first to define briefly just what we shall mean in this

⁹⁰ URBACH, E. and GOTTLIEB, P. M. *Am. Rev. Tuberc.* 44: 298, 1941.

⁹¹ RICH, A. R. *Physiol. Rev.* 21: 6, 1941.

discussion by the word immunity. Pinner²² correctly calls attention to the fact that the term is being employed in a rather facile manner: "Instead of a generally accepted definition of immunity there exist at the present time a multiplicity of uses and a general vagueness."

We shall employ the term in the following sense. The *immune* organism, in contrast to other individuals of the same or of another species, is in a state of specific, increased resistance to or tolerance of the action of pathogenic agents and/or their products. This state of immunity is manifested by a total or relative insensitiveness to the introduction of foreign substances into the organism. This absence of reactivity may be a characteristic of a species or a race, and may also be an innate characteristic of the individual. This latter state, caused by inability to produce antibodies in reaction to bacteria or viruses, is termed *natural anti-infectious immunity* or preferably *natural refractory state*. However, when the immunity is acquired, either actively as a result of disease or vaccination, or passively by the transfer of antibodies, it is termed *acquired anti-infectious immunity*. Such passive transfer of antibodies may occur *in utero* by way of the placenta, in the neonatal period by the mammary route in the maternal milk or colostrum, or artificially by the injection of antiserum derived from an actively immunized animal or individual.

In accordance with the special characteristics of exotoxin-producing organisms, we speak of *natural antitoxic immunity* or preferably *natural resistance to toxin*, and of *acquired antitoxic immunity*.

In considering the general problem of anti-invasive or antibacterial immunity, Mudd²³ points out that the ability of a pathogenic agent to establish itself on and to invade its host doubtless depends on the whole complex of relationships between parasite and host. Specific active and passive immunity against invasiveness, however, is dependent primarily on the antigens at the surface of the pathogen. Studies with the electron microscope confirm this opinion. The specific neutralization by antitoxins of the bacterial metabolites called

exotoxins constitutes another form of immunity.

We shall first turn our attention to the acquired anti-infectious or so-called *reinfection immunity*. This type of immunity is brought about by the production of a series of specific protective substances (e.g., agglutinins, precipitins, opsonins, lysins, tropins, etc.) formed under the influence of the specific excitants of the given infectious disease.

Immunity against infectious agents is not a state of insensitiveness, but rather a state of hypersensitiveness to constituents and metabolic products of the bacteria. This is clearly shown by the high content of antibodies found in the blood of immunized human beings and animals. Other experimental investigations described here permit us to assume that ana-

TABLE 2—*Relationship of Anaphylaxis and Immunity Their Dependence on the Immune State of the Animal and the Conditions of Reinfection*

	Tuberculous Guinea Pig	Normal Guinea Pig
Reinfection with large dose of tubercle bacilli (intravenous)	death after several hours— anaphylaxis	remains well for days, becomes sick only after a week
Reinfection with very small dose (subcutaneous)	no change in condition—immunity	evidences primary complex of tuberculosis after 2 to 3 weeks

phylaxis and immunity are to be regarded as only quantitatively different types of reaction based on the same fundamental state.

Metalnikov sensitized guinea pigs with killed cholera vibrios. These animals were then able to tolerate without reaction the subcutaneous administration of a dose of living cholera vibrios lethal to nonsensitized animals—an example of immunity. On the other hand, subcutaneous administration of large doses of vibrios or small intravenous doses resulted in anaphylactic death. Hamburger²⁴ made similar observations in tuberculous guinea pigs, as shown in Table 2.

According to Topley and Wilson,²⁵ the difference between the anaphylactic and the immune

²² PINNER, M. *Am. Rev. Tuberc.* 33: 173, 1931.

²³ MUDD, S. *J.A.M.A.* 126: 632, 1941.

²⁴ HAMBURGER, F. *Wien klin. Wchnschr.* 46: 9, 1933.

state is quantitative rather than qualitative, but depends upon the balance between circulating and fixed antibodies. The anaphylactic state is associated with the presence of fixed antibodies and the absence of circulating antibodies. The immune state is associated with the presence of circulating antibodies in a concentration sufficient to protect the fixed antibodies that are also present.

These facts prove that anaphylaxis and acquired anti-infectious immunity are varying expressions of the same biologic process—namely, of hypersensitiveness, and these manifestations of hypersensitivity can be reproduced at will provided that certain definite experimental conditions are maintained as regards the quantity and manner of administration of antigen.

In contrast to this opinion a number of authors—especially Rich⁹⁵—have advanced the theory that immunity and allergy are entirely independent and dissociable phenomena. On the basis of animal experiments Rich⁹⁶ and his collaborators⁹⁷ have arrived at the following conclusions:

(1) Immunity can be distinguished from allergy by four methods: (a) establishment of active immunity without concomitant development of allergy; (b) passive transfer of immunity without transfer of allergy; (c) persistence of immunity after abolition of allergy by desensitization or after a spontaneous decline in sensitivity; (d) an apparent lack of parallelism between immunity and hypersensitiveness.

(2) Inhibition of the spread of bacteria in the immune body is not dependent upon allergic inflammation, as has been generally assumed, but is effected primarily by the action of immune antibodies.

(3) Allergy can be established without immunity, acting alone, it lowers resistance to infections.

Nowhere is the difficulty of finding clear answers to these problems better illustrated than in the contradictory results obtained in experiments on tuberculosis in guinea pigs.

Rich demonstrated that guinea pigs immunized against tuberculosis lose the capacity to react cutaneously to high doses of old tuberculin and that this loss of reactivity in no way influences the animals' immunity to superinfection. These findings were confirmed by Siegel, Selter, Weiland and others. Corper and his associates^{98, 99} also reported that the allergic skin reaction may be entirely absent in guinea pigs that still retain their specific immunity to tuberculosis, and vice versa. More recently, Corper and Cohen¹⁰⁰ found that attempts to desensitize tuberculo-bacillary hypersensitive guinea pigs by repeated subcutaneous injections of heat-killed tubercle bacilli were unsuccessful. Intravenous administration caused depression of cutaneous allergic hypersensitivity to both tuberculin and bacillary bodies but had no effect on the course of the tuberculous infection. Woodruff and Kelly¹⁰¹ on the other hand observed that tuberculous guinea pigs which spontaneously lost their skin sensitivity to tuberculin before death showed extensive pulmonary lesions containing large numbers of acid-fast bacilli along with pathologic changes in the spleen while those which retained a high degree of tuberculin sensitivity before death showed few or no acid-fast bacilli in their pulmonary lesions. However, Steiner and Zuger¹⁰² showed that in guinea pigs inoculated with a dissociated avirulent human strain of tubercle bacillus skin sensitivity gave no indication of the presence or absence of immunity to reinfection with a virulent homologous strain. In a study of guinea pigs vaccinated with BCG and subsequently desensitized with tuberculin Geeve¹⁰³ found that the desensitized vaccinated animals showed no corresponding decrease in immunity in comparison with allergic vaccinated animals, and concluded that the skin reaction is a more accurate index of the allergic state in this species than is the general (thermal) response.

Birkhaug¹⁰⁴ like Rich, maintains that the

⁹⁵ RICH A. R. *Acta paediat* 16: 1 1933

⁹⁶ Idem JENNINGS F. B. JR. and DONNING L. M. *Bull Johns Hopkins Hosp* 33: 172 1933

⁹⁷ ROTHSCHILD H. FRIEDENWALD J. S. and BERNSTEIN C. *ibid* 54: 232 1934

⁹⁸ CORPER H. J. COHEN M. L. and DAMEROW A. P. *Am J Clin Path* 19: 361 1940

⁹⁹ CORPER H. J. and COHEN M. L. *J A M A* 112: 403 1939 *Am Rev Tuberc* 45: 293 1941

¹⁰⁰ Idem *Am J Clin Path* 14: 344 1944

¹⁰¹ WOODRUFF E. and KELLY R. G. *J Immunol* 45: 79 1942

¹⁰² STEINER M. and ZUGER B. *ibid* 46: 83 1943

¹⁰³ GEEVE E. F. *Am J Clin Path* 12: 606 1942

¹⁰⁴ BIRKHAUG K. E. *Acta tuberc Scand* nov 13: 221 1939

mechanisms underlying tuberculosis hypersensitiveness (allergy) and acquired resistance to tuberculosis (immunity) are two distinct phenomena. Thomas and Duran-Reynolds found that the rabbit, although exhibiting little skin hypersensitiveness to tuberculin, has marked resistance to superinfection; while the guinea pig, in spite of marked skin reactivity, has relatively little tissue immunity. The discrepancy between immunity and allergy has also been shown to exist in relation to other micro-organisms. Angevine showed that rabbits evidence considerable skin sensitivity but scant immunity when injected hypodermically with relatively avirulent cultures of hemolytic streptococcus; on the other hand, when a culture made more virulent by animal passage was injected, the result was little skin sensitivity but high immunity. Sabin and Joyner demonstrated that guinea pigs highly sensitized to tuberculo-protein did not show the Koch phenomenon when inoculated with living tubercle bacilli. Furthermore, clinical experience has shown that skin allergy in man fluctuates widely in tuberculous individuals and is in no way related to the clinical outcome.

Although all these experimental and clinical observations are unquestionably accepted, the conclusions reached by Rich and his school have become the subject of extraordinary controversy. Most of the disagreement is due to the fact that Rich tends to narrow his concept of allergy to the extent of having it signify almost exclusively the acquired hypersensitiveness of the skin.

In a penetrating analysis of these rather confusing experimental results, Pinner¹⁰⁵ points out that much ingenious work has been vitiated by poor logic due to a terminologic chaos. He emphasizes that the relation of immunity to allergy is not a simple quantitative function and that one is not the measure of the other. Whether an allergic (that is, an infected) animal is proved to be immune or hypersensitive to reinfection depends to a large measure on the experimental set-up. He adds that the high morbidity rate in the process of "desensitization" leading to a rigid selection of the survivor group, the confusion between true

"desensitization" and mere abolition of the local cutaneous inflammatory response, and differences in the pathologic findings depending on the stage of the reinfection disease account for some of the difficulties of interpretation.

Schick,¹⁰⁶ the distinguished collaborator of von Pirquet, charges that "Rich identified hyperergic reaction with the whole of allergy." In his opinion, the fact that Rich was able to destroy skin sensitiveness without eliminating the manifestations of increased resistance, clearly demonstrates that skin sensitiveness is only one part of the phenomenon of allergy—just as the anaphylactic reaction or the hypersensitiveness following smallpox vaccination constitutes only a very small part of the totality of allergy. As Schick puts it, "even Rich has to admit that his idea of the separation of immunity from allergy is based on the fact that he has abandoned the original meaning of allergy, defined by von Pirquet as an 'altered reactivity.'"

Pagel¹⁰⁷ claims, in agreement with Rich, that the phenomena of tuberculin allergy and of immunity against tuberculosis can appear independently of each other. In opposition to Rich, however, Pagel believes that these two phenomena represent different degrees of the same fundamental allergic process. Similarly, Siegel¹⁰⁸ concludes that tuberculin hypersensitiveness and immunity to reinfection are concomitant manifestations, and that each is the result of allergy produced by a previous injection. Hyposensitization by means of increasing doses of tuberculin serves to suppress one form of allergic reaction, namely, the tuberculin hypersensitiveness, while the second form, the immunity, is preserved.

Kallós¹⁰⁹ raises the interesting question whether the specific nonreactivity of the skin in a patient with bacterial infection is an expression of a positive energy. This refers to the well-known fact that in infectious diseases such as tuberculosis, patients in very good physical condition may show an incapacity to react cutaneously to tuberculin.

¹⁰⁵ SCHICK, B. *Radial Rev. & Mississippi Valley M. J.* 59, 1, 1937.

¹⁰⁶ PAGEL, W. *J. Path. & Bact.* 44, 645, 1937.

¹⁰⁷ SIEGEL, J. *Beitr. a. Klin. d. Tuberk.* 84, 311, 1934.

¹⁰⁸ KALLÓS, P., and KALLÓS-DEFFNER, L. *Erebn. d. Hyg. & Bakt., Immunitätsforch. u. exper. Therap.* 17: 76, 1935.

¹⁰⁹ PINNER, M. *Pulmonary Tuberculosis in the Adult*. Springfield, Ill.: Thomas, 1945.

As is now recognized by many investigators the skin of these patients contains specific antisustances called anticutines

Bronfenbrenner¹⁵ concludes that the phenomena of experimental anaphylaxis of clinical hypersensitiveness, and of specific acquired resistance to infection are all the result of a single underlying mechanism, and that the character of the entire observable reaction is determined by secondary factors. According to Bieling and Oelrichs,¹¹⁰ only one important fact stands out as a result of Rich's experiments—the development of immunity is not associated with a hyperergic tissue reaction. Pinner²² is therefore right—and this appears to us to be one of the chief results of this scientific controversy—in warning the clinician not to attempt to correlate a strong tuberculin reaction with a high degree of immunity, and vice versa. "Hypersensitivity [of the skin] is not an index of immunity."

In regard to the special question of the relationship between allergy and immunity in tuberculosis, there are two diametrically opposed viewpoints, one represented by Calmette and his associates, who favor attempting to produce artificially a condition of allergy to tuberculo-protein in human beings, the other represented by Rich and his school, who believe that allergy is injurious to the tuberculous organism, and that every attempt should be made to abolish an allergic state. Rich recommends, therefore, that tuberculin therapy be carried out so energetically that complete desensitization will result. Birkhaug¹¹¹ introduced the term "lathergic immunity" to denote that a tuberculous organism has been rendered insensitive to tuberculin by means of desensitization. Woodruff and Willis¹¹² tested this point by means of animal experiments, and are convinced that opinions are controversial because of such variables as the dose of tuberculin, the duration of tuberculin treatment, the dose of bacilli, the time of inoculation with bacilli in relation to the first tuberculin injection, and infection and trauma in the injected animals. Animal experiments convinced these authors that at

least a partial reciprocal relationship exists between the allergic state of infected guinea pigs and the number of tubercle bacilli demonstrable in their lungs. And when Rich charged that "there has never been one single experiment or observation placed on record, through which hypersensitivity has been shown to be necessary for protection in any stage of any infection under any condition whatsoever," Woodruff and Willis replied. While no unequivocal proof has been adduced that allergy is essential to protection, the fact remains that in such diseases as tuberculosis and smallpox, protection has never been conferred either experimentally or in the clinic, without first producing the hypersensitive state."

Cohen¹¹³ points out that apparent differences in the phenomena of infectious disease and of clinical allergies are due to variations in the chemical structure of the antigens and their availability for contact with the tissues. In both infectious disease and clinical allergy, it is the antigen-antibody union which causes the release of toxic materials, and it is these materials which produce the local reactions and the clinical disease. In the infectious diseases, the nature of the toxic material formed is determined by the chemical nature of the antigen. In the clinical allergies, the same toxic material is formed from the tissues, no matter what antigen is the determinant for the specific reaction. This accounts for the similarity of symptoms in the clinical allergies from a wide variety of antigens and for the diversity of the clinical and pathologic findings in the infectious diseases. The terms hypersensitive, hyposensitive, anergic and immune are merely expressions of a quantitative relationship between the antigen and its corresponding antibody.

There can be no doubt that immense progress would be made in combating bacterial hypersensitiveness if it were possible to find methods of desensitizing the organism without diminishing its immunity. One need only consider what it would mean in the treatment of tuberculosis if one did not have to fear allergic reactions (edema, inflammation, and necrosis). Unfortunately, however, the meth-

¹¹⁰ BIELING R. and OELRICHS L. *Beitr z Klin d Tuberk* 99: 491, 1937.

¹¹¹ BIRKHAUG K. *Acta tuberc Scandnav* suppl 5, 1940.

¹¹² WOODRUFF C. E. and WILLIS H. S. *J Immunol* 37: 549, 1939.

¹¹³ COHEN M. B. *J Allergy* 14: 116, 1943.

ods that Rich and his school employed in animal experiments are not yet available for use in human therapy. But of even greater importance is the fact that when the administration of tuberculin to the experimental animal is interrupted, there is a gradual return to the former state of hypersensitiveness—in other words, the desensitization is not permanent.

Here it is in order to discuss briefly the question of *local immunity*. This term designates the resistance of a tissue or of an organ to infection, while the body or host as a whole may present little or no immunity to the same offending micro-organism. There appears to be very little agreement as to the mechanism of production of local immunity. Harris¹¹ has undertaken a comprehensive analysis of the reasons for and against the humoral and cellular concepts, as well as of the possibility of a local specific hyposensitization process. Besredka¹² heads the school holding that local tissue immunity is independent of antibodies and phagocytosis. While such a thing as an acquired local immunity might very possibly exist, it would seem doubtful whether this mechanism of local resistance could exist without the production of antibodies. More recent investigations seem to show that this form of immunity is based not so much on free antibodies circulating in the blood as on locally produced sessile antibodies (Torikata and Imaizumi,¹³ Cannon and collaborators¹⁴).

Having dealt, up to this point, only with anti-infectious immunity, we turn now to *antitoxic immunity*. This state exists when an organism, after receiving injections of small doses of a given toxin, and after a certain period of time (the latent period for production of antitoxin), becomes either hypo- or insensitive to subsequent administration of the same toxic substance (active antitoxic immunity). A similar sequence of events occurs during infection with toxin-producing bacteria. This immune state can be passively

transferred (passive antitoxic immunity) by the administration of antitoxin-containing serum.

The union of antigen and antibody *in vitro* takes place in the form of precipitation. The same union in the living tissues manifests itself by local inflammation. These conditions are reversed, however, in the toxin-antitoxin reaction. *In vitro*, the union of toxin and antitoxin takes place practically without any precipitation. *In vivo*, when the organism has a sufficiently high antitoxin titer, the action of the toxin is nullified, and no cytotoxic effect ensues in the tissues. Thus, for example, diphtheria toxin (Schick test) and the toxin of the scarlatinal streptococcus (Dick test) cause inflammation of the skin only in non-immune individuals, whereas a negative result demonstrates the presence of antitoxins.

2. ALLERGIC HYPOSENSITIVENESS

Hypo-ergy and anergy constitute this group.

Hypo-ergy denotes freedom from clinical manifestations or decided improvement in a hypersensitive organism following hyposensitization measures. Hypo-ergy depends on an increase in the supply of free antibodies circulating in the blood. It is now assumed that the mechanism consists of the neutralization of the antigen in the blood stream, with the result that the tissues are spared the effects of the antigen-antibody reaction; this would explain the absence of allergic manifestations. Although this is the generally accepted explanation, it does not accord with a great deal of experimental and clinical observation (Samms,¹⁵ Bronfenbrenner¹⁶). Some of these facts will be considered below (p. 91). In any case, such a state is called "hypo-ergy" and not "anergy," since administration of very large quantities of antigen can still produce severe manifestations of hypersensitiveness. Hypo-ergy is thus a condition of only relative insensitiveness. The fact that skin tests with the given antigen almost invariably elicit positive reactions, is another indication of the existence of a potential hypersensitiveness.

The term *anergy*, on the other hand, denotes the absence of reaction to a given antigen, e.g.,

¹¹ HARRIS, W. H., and WALTHER, S. *South M J* 33 925, 1910

¹² BESREDKA, A. *Local Immunization* Baltimore Williams & Wilkins, 1927

¹³ TORIKATA, R., and IMAIZUMI, M. *Ztschr f Immunitätsforsch u exper Therap* 94 342, 1939

¹⁴ CANNON, P. R., and SULLIVAN, F. L. *Proc Soc Exper Biol & Med* 29 517, 1937; WALSH, T. E., SULLIVAN, F. L., and CANNON, P. R. *ibid*, p. 675.

¹⁵ SAMMS, F. E. *J. Allergy* 15, 414, 1944

¹⁶ BRONFENBRENNER, J. *Ann Allergy* 2 472, 1944.

to a bacterial antigen such as tuberculin or trichophyton. This anergy of the skin as well as of the entire organism is regarded as specific (positive) or nonspecific (negative), depending on whether the individual is in very good or very poor physical condition.

Specific (or positive) anergy is encountered particularly in tuberculous individuals who are in a state of healing. A special group comprises certain types of cutaneous or visceral tuberculosis known as sarcoids; these cases are distinguished by the absence of a reaction even to large doses of tuberculin. The results of recent investigations now permit us to include hormone refractoriness in this category (Collip¹¹⁰).

Grossmann would prefer the term "anergy of healing" to "specific anergy." According to J. Jadassohn, Naegeli, and other authors, this state arises when an equilibrium between antigen and antibodies has been reached. It is of little importance whether the total amount of antigen and antibody is great or small, provided the difference between them is so insignificant as to prevent an antigen-antibody reaction. As evidence of an increased antigen content in the tissues, the so-called "anticutines" (see p. 460) can be demonstrated in the sarcoid types.

Nonspecific (or negative) anergy is a characteristic of cachectic patients, whence the not uncommon designations of "cachectic anergy" and "anergy of exhaustion." This state is encountered in such severe acute forms of tuberculosis as meningitis, pneumonia, and military tuberculosis, as well as in all diseases that entail cachexia (sarcoma, cancer, pernicious anemia). Furthermore, during the eruptive stage of a great many infectious diseases such as measles, scarlet fever, epidemic meningitis, and secondary syphilis, the reactivity of the skin to tuberculin will be definitely reduced. Similar observations have been made with regard to the Schick and Dick tests. Moreover, Mackenzie and Hangar have shown that, in human beings, allergy to the derivatives of the streptococcus is often diminished during the febrile periods of typhoid and pneumonia. Hangar has also reported a striking diminution—during severe acute in-

fections—of the usual skin reactivity of rabbits to *Pasteurella leptoseptica*.

The group of negative anergy might also include certain anergic states observed in the course of syphilis. Such states may appear in early syphilis in the form of a decreased resistance to spirochetes, a condition known as "precocious tertiarism" of malignant syphilis. Furthermore, a state of anergy has frequently been held responsible for fastness to therapy, as in syphilis of the central nervous system. To combat this condition various metasppecific therapeutic measures (e.g., tuberculin, typhoid, and fever therapy) have been successfully employed. These measures are intended to remove the state of anergy by means of metasppecific stimulation of the antibody mechanism (see p. 211).

Various theories have been advanced to explain the mechanism of nonspecific anergy. This condition, according to J. Jadassohn, is attributable to the incapacity of the antibody-producing system to react. Naegeli rejects the idea that there is any lack of antibodies and claims that, as a result of the flooding of the organism with bacteria, there is merely an inadequate production of protective antibodies. According to Sulzberger,⁴ this non-reaction is due to the absence, reduction, or inhibition of some nonspecific factors essential for the production of skin reactions.

C. HETERO ALLERGY (HETERO ALLERGIC PATHOLOGY)

The term *hetero-allergy* (1925) was originally used by Dujardin and Decamps¹²¹ to denote the fact that allergizing diseases (tuberculosis, syphilis, intercurrent staphylococcal infections, etc.) are able to heighten the manifestations of unrelated latent allergies. More recently Weissfeiler¹²² (1934) has used the term in a modified sense to indicate a changed reactive capacity of the tuberculous organism in relation to other bacteria. This is almost synonymous with the definition given below of *metallergy*, a concept introduced by the senior author¹²³ in 1934.

¹²¹ DUJARDIN, B. and DECAMPS, N. Arch. internat. de med. exper. 1: 339, 1925.

¹²² WEISSFEILER, J. Ztschr. f. Immun.-forsch. u. exper. Therap. 83: 263, 1934.

¹²³ URBACH, E. Klin. Wchnschr. 13: 1417, 1934.

¹¹⁰ COLLIP, J. B. J. Mount Sinai Hosp. 1: 28, 1934. Idem. SELYE, H. and WILLIAMSON, J. E. Endocrinology 23: 279, 1938.

Hetero-allergy is indeed a very useful name, since its derivation clearly expresses the fact that the allergic manifestations in such cases are due to a different (*hetero-*) allergen. However, there are two basic types of hetero-allergy namely:

(1) *Parallergy*, when the allergic organism reacts to another inciting agent with a manifestation of hypersensitiveness *different* from that elicited by the original sensitizing allergen;

(2) *Metallergy*, when the hypersensitive organism responds to another inciting agent with an allergic reaction of the *same type* as originally present.

TABLE 3—Differences between Metallergy and Parallergy

Parallergy	Metallergy
Clinical manifestations different from original reaction	clinical manifestations same as original reaction
Flare up reaction never	flare-up reaction often
Occurrence only during development of allergy or during great allergic oscillations	occurrence independently of allergic state present
Never re-elicitable	re-elicitable often, leading to a polyvalent non specific pathergy

It will be seen that although both *parallergy* and *metallergy* are heteroallergic in nature, they differ basically in their clinical manifestations and other important characteristics (see Table 3).

The basic differences between the concepts of *parallergy* and of *metallergy* may be summarized as follows. (1) In *parallergy* the clinical manifestations in response to the second allergen are different from those in response to the first, while in *metallergy* they remain the same. (2) In *parallergy*, a "flare-up" effect is impossible because the phenomena never occur at the site of the primary allergic reaction; the reaction in *metallergy* is based upon a flare-up mechanism. (3) *Parallergy* occurs only at the time of the development of allergy or of great fluctuation in the state of hypersensitivity, while *metallergy* may accompany

but does not require a momentarily strong allergic reaction—is, in short, more or less independent of the allergic state present at the moment. (4) The *parallergic* conditions can never be evoked a second time, while the *metallergic* state may be repeated at will.

For these reasons we suggest hetero-allergy as the inclusive designation, but, since it does not differentiate between *parallergic* and *metallergic* manifestations, there is in addition a definite need for the more specific terms.

The concepts of *parallergy* and *metallergy* may be of advantage in clarifying a number of well-known but hitherto inexplicable phenomena and questions, as for example: (1) the flare-up of allergic reactions on exposure to apparently nonspecific agents; (2) the significance of positive allergic skin reactions to substances or extracts that certainly cannot be considered as the specific allergens responsible, (3) the "broadening" of sensitization during the period of acute allergic symptoms, and also during the period of their decline, (4) the transition of a specific allergy into a polyvalent metaspecific allergy (*metallergy*) and finally into a nonallergic pathergy; (5) the pathologic mechanism of infantile dermatitis; (6) the quasi-specific mechanism of apparently nonspecific methods of treatment, such as tuberculin or peptone injections.

1. PARALLERGY

Moro¹²⁴ and Keller¹²⁵ employed the term *parallergy* to denote the fact that, during the development of an allergy or during states of considerable allergic fluctuation, a specifically sensitized organism will react more easily and more rapidly to a given living or nonviable excitant than will a nonallergic organism. As shown by the examples submitted by them (see below), *parallergy*, as they first defined the term, denotes the fact that other specific antigens or germs are able to elicit in a specifically sensitized organism, during a given state of reactivity, clinical manifestations different from those induced by the first antigen.

Several years later these investigators¹²⁶ broadened their concept of *parallergy*. It was then made to embrace the phenomena that

¹²⁴ Moro, E. *Monatsschr f. Kinderh.* 31 193, 1926

¹²⁵ Keller, W. *Deutschemed. Wchnschr.* 54 327, 345 1928

¹²⁶ Moro, E., and Keller, W. *Klin. Wchnschr.* 14 1, 1935

Urbach had in the meantime designated as metallergy.¹²³ Their second definition of parallergy connotes a nonspecific alteration of reactivity on the basis of a previously specific allergy; the agents may be living or nonliving. Such a state of parallergy may or may not accompany allergy. It is most frequently expressed by an increased tendency to inflammation and occurs most markedly at the time of development of the allergy and during periods of its fluctuation. However it may also develop during a static phase of the allergic condition.

Quite recently numerous attempts have been made (Roessle, Keller) to divest the concept of parallergy of its special character and to regard it only as representing one type of nonallergic pathergy. We most emphatically reject this viewpoint for there is a fundamental difference between heteroallergic and nonallergic pathergy.

The concept of parallergy is to be distinguished from that of biotropism (as established by Milian¹²). In parallergy one must postulate the existence of an allergic state as essential for the effectiveness of other antigens or bacteria. In biotropism on the other hand one presupposes a nonspecific decrease in resistance—brought about either by a toxic condition or by physical or chemical agents—and this decreased resistance of the organism permits previously latent infectious agents to become active or a saprophytic microorganism to become pathogenic. A typical case of what Milian terms biotropism is a morbilliform rash following the second injection of arsphenamine and assumed to be due to activation of the virus of measles already present in latent form.

Parallergic Hypersensitiveness

Von Pirquet formulated the laws of allergy largely on the basis of observations of the typical course of serum sickness and of the sequelae of smallpox vaccination. Similarly Moro established the concept of parallergy after studying atypical manifestations following vaccination. When tuberculin negative children are vaccinated against smallpox renewed cutaneous testing with tuberculin

will elicit positive reactions during the height of the vaccinal reaction (i.e. from the ninth to the twelfth day). In a similar manner tuberculin negative children will give a positive intracutaneous tuberculin reaction after a serum injection—an immunobiologic phase analogous to that after vaccination. Likewise the onset of sensitivity to cow's milk in an infant may be the cause of a positive tuberculin reaction—a state of reactivity that may last for the duration of the milk hypersensitiveness (Freund). Other authors have reported temporarily positive Schick and Dick reactions after vaccination and varicella. Even the traumatic reaction to the control injection which usually disappears very promptly occasionally persists in these individuals for more than twenty-four hours and is surrounded by a fairly wide inflammatory area.

Thus in the period of development of allergy vaccinated or otherwise allergized individuals respond with positive skin reactions to various excitants. These responses however do not present the clinical picture characteristic of the basic allergizing disease (e.g. vaccinia vesicles or local serum reaction); they correspond rather to the action of the second antigen (tuberculin, diphtheria toxin, etc.).

These examples illustrate the effects of artificial administration of heterogenous substances. The same results are observed clinically under natural conditions of exposure. Moro and Keller present as examples the vaccinal angina that always appears during the critical period of areola formation (ninth to eleventh day) and the form of tonsillitis that appears from seven to nine days after serum injections (Koenigsberger). These infections are assumed to occur for the following reasons. The organism is normally not sensitive to the bacteria resident in the tonsils, but an alteration in its state of sensitivity tends to reduce its powers of resistance and the bacteria are now able to cause tonsillitis. Similarly regarded are postvaccinal attacks of appendicitis, vaccine encephalitis—which occurs in the great majority of cases from the ninth to the twelfth day after vaccination—and the encephalitis complicating measles which usually first appears between the fifth and seventh day after the exanthem. Wallgren includes

here erythema nodosum of children. This condition almost invariably appears at the time of transition from the preallergic to the allergic phase—about seven weeks after tuberculous infection, and simultaneously with the first manifestation of sensitivity to tuberculin. Brandt reports an exanthem resembling erythema multiforme occurring ten days after vaccination, and calls this condition "parallergic vaccination exanthem." Moro and Keller also consider the phlyctenulas, as well as the secondary infiltrations of the lungs (Redecker) arising in connection with grippe, whooping cough, and measles, partly as manifestations of parallerger.

Veil as well as the senior author has shown in detail how the concept of parallerger can serve to explain the observation that usually harmless bacteria may become pathogenic in an organism that has been allergized by infection, especially by focal infection, and that these newly pathogenic micro-organisms can cause acute appendicitis, cholecystitis, pyelitis, cystitis, and even bronchopneumonia. It would seem likely that certain mixed infections might be included here, along with the sequelae more or less regularly marking the course of certain conditions, such as nephritis following scarlatina, or otitis media following measles. Furthermore, von Bergmann includes in this category the activation of latent inflammation in sensitized tissues. Thus, a quiescent cholecystitis may flare up after a tonsillitis although there may be colon bacilli, for example, in the gallbladder, and streptococci in the tonsils.

The fundamental animal experiments of Bieling and Oelrichs¹²³ constitute one of the main supports for the clinical concept of parallerger. They demonstrated that when tuberculo-allergic animals are tracheally superinfected with bacteria that are in themselves harmless (e.g., colon bacilli), the lungs will show considerable infiltration and even outright cavitation. On the other hand, similar infection of nontuberculous animals will produce insignificant results. Likewise, intratracheal administration of *Treponema pallidum* in tuberculo-allergic rabbits causes reactive changes of pneumonic character. Weiss-

feiler¹²² observed a similar effect of acid-fast saprophytes, actinomycetes, diphtheroids, and sarcinae in tuberculous animals.

All these experimental studies have one significant point in common—that micro-organisms having nothing to do with the initial allergization of the organism are capable of eliciting rapid reactions. The course of such reactions appears to depend upon the nature of the second micro-organism involved, as well as upon the time element.

These few examples will serve to make it clear that the concept of parallerger is of importance in explaining the mechanisms of various diseases, particularly of morbid processes appearing as sequelae of infectious diseases.

Parallerger Hypo- and Insensitiveness

It has been pointed out that vaccination and certain infectious diseases may, under certain conditions, lead to positive skin reactions to nonspecific excitants, and also to the acquisition of pathogenicity by ordinarily harmless saprophytic micro-organisms. Similarly, there are phases in the course of these allergic and allergizing diseases during which precisely the opposite can be observed—hetero-allergic hypo- and insensitiveness. These must be further subdivided into the parallerger and metallerger types. This distinction cannot be based on differences in clinical manifestations, because we are dealing with a partial or complete lack of responsiveness to the second agent. Hence we must rely on the second important differentiation between parallerger and metallerger, i.e., the duration of the induced reactivity. We consider hypo- or insensitiveness parallerger when it is confined to a brief period—a few days—during the development of an acute allergic state, such as occurs in the exanthems. On the other hand, we speak of metallerger hyposenitiveness when the condition is rather persistent, as for instance in successful hyposenitization therapy (for examples, see p. 30).

The experiments of Ricciardi will serve as examples of parallerger hyposenitiveness. A group of tuberculous infants were tested and gave uniformly positive reactions to tuberculin. Four days later, prophylactic vaccination was performed. After another six days, the

¹²³ BIELING, R., and OELRICHS, L. *Ztschr. f. Tuberk.*, 69: 742, 1934.

cutaneous tuberculin tests were repeated. About one third of the cases then showed a definitely weakened reaction and some of these cases showed no reaction whatsoever. Ricciardi obtained similar results with children suffering from varicella. It has long been known, of course, that a great variety of infectious diseases such as measles, scarlatina (von Pirquet), typhoid fever and meningitis will temporarily reduce skin sensitiveness to tuberculin, to variola vaccine and to *Bacillus coli* vaccine, as well as to nonspecific irritants such as codeine (Pilcher).

But this parallergic hypo and insensitive ness is by no means restricted to skin reactions. Thus, anaphylactic shock released by a specific reaction may also cause an increased non specific resistance to the foreign agents of infection (Bieling¹⁹). The occurrence of a strictly specific shock renders the organism temporarily incapable of reacting to other antigens. A comparable condition is found in human beings. In allergic individuals intercurrent acute infectious conditions (e.g., erysipelas) may, for a while, totally eliminate the usual allergic symptoms.

It seems to us that Naegeli has offered the best explanation of parallergic hypo and insensitiveness. An organism engaged in combating an infection (e.g., measles), is not in a position at the same time to create a sufficient number of antibodies to another antigen, such as tuberculin. Temporarily, therefore, there can be no specific antigen antibody reaction in the form of a tuberculin reaction.

2 METALLERGY

The term *metallergy* was introduced by the senior author²⁰ to denote the fact that a specifically sensitized organism—one in which the allergic condition is usually of long standing, and in which clinical manifestations are usually mild—will respond to subsequent exposures of a different nature (to so called metallergens) with *specific allergic reactions* presenting the *same clinical picture* as that elicited by the first allergen. In other words the specific (e.g., tuberculous) antibody reacts to an unrelated antigen precisely as though it were a specific one. We have sug-

gested that such antigens be named *metantigens**. Metallergy would appear to be based on a 'metantigen antibody' reaction.

Metallergic Hypersensitiveness

The following animal experiments reveal the fact that actually metantigens can produce a metantigen antibody reaction with a resulting increase in the number of *specific* antibodies. According to Mackenzie and Fruehbaumer²¹ rabbits that have been sensitized to egg white will after a while show no trace whatsoever of circulating antibodies to egg in their blood; these antibodies will immediately reappear however after injection of a typhoid vaccine. Mackenzie and Fruehbaumer called this phenomenon an *anamnesic reaction*. For years Weichardt²² has stressed the fact that allergized cells can react to non specific excitants with specific activities. In other words that a specifically conditioned organism can be stimulated by means of non specific influences to produce specific antibodies as proved by an increased titer of specific antibodies in the serum. Bieling²³ made a similar demonstration in bacterial allergy in guinea pigs immunized with a given type of bacteria; he found that after several weeks the antibody content and the immunity were considerably reduced. On the other hand the production of specific antibodies could be induced by means of other antigens not belonging to the same group of bacteria, this occurred very promptly, some hours later. There can surely be no question here of any *specific* antigen antibody reaction. Also the experiments of Landsteiner and van der Scheer²⁴ indicate that one antigenic grouping can elicit the formation of diverse antibodies. We must assume therefore, that the new antibody production is

* Years ago Cantani employed the term metantigen to designate substances that are produced within the organism as a result of the transformation of endogenous substances by autolytic or degenerative processes thus acquiring antigenic function. Such substances are now generally called endogenous allergens. We therefore feel that it is permissible to employ the term metantigen in the sense mentioned above.

²⁰ MACKENZIE G. M. and FRUEHBAUMER E. Proc. Soc. Exper. Biol. & Med. 24: 419, 1927.

²¹ WEICHARDT W. Handb. d. path. Mikrob. 1 (pt. 2): 1147, 1929.

²² LANDSTEINER K. and SCHEER J. VAN DER. J. Exper. Med. 71: 445, 1910.

elicited by an excitant that is not nonspecific but rather metaspecific in its action.

Parker¹²³ showed that immune rabbits possess a greater reactivity to a heterogenous antigen than do normal animals. He reported that rabbits sensitized to staphylococcus or to horse serum developed precipitins against giant ragweed pollen ten days after the first intraperitoneal injection of the whole unground pollen suspended in salt solution.

These animal experiments all serve to support the view that antibodies can combine not only with the specific antigen, but also with other agents, although not in such a perfect combination. It seems likely that an organism with a high antibody content will more readily react to another antigen (metantigen) than will an organism poor in antibodies. This might very well explain why not a few allergic conditions in the human species gradually suffer a loss of specificity—a state that we may designate as metallurgy as long as only a few allergens are involved.

The concept of metallurgy enables us readily to explain, with regard to the question of specificity, numerous hotly disputed allergic phenomena, especially the so-called nonspecific flare-up in human beings and in animals. We refer to the well-known fact that tuberculin reactions, for example, in human beings and in animals can be made to flare up by a great many excitants such as bacterial vaccines, trichophyton, milk, peptone, horse serum, broth, histamine, and even autogenous serum and ultraviolet irradiation. Similarly, healing or completely healed patch test sites (e.g., poison ivy) may be "lighted up" by the application of nonspecific oleoresins in adhesive tape. Such flare-ups will also be seen following positive Dick, Schick, and tuberculin reactions (Shelmire¹²⁴). In this connection, Ferry¹²⁵ reports an especially interesting observation. During the course of measles in an adult, a circumscribed area of redness developed at the sites of previous injections of scarlet fever toxin (Dick test).

The following instances should also be mentioned here. Exposure to trichophyton or to luetin can sometimes cause the focal relighting of a tuberculoderma, and a tuber-

culin injection can produce a focal reaction in a lesion of leprosy or in a syphiloderm.

A third group embraces heterologous bacterial hypersensitivenesses. This type of hypersensitiveness is exemplified by the following experiment. In rabbits prepared intracutaneously with horse serum, a second injection of any type of bacteria three weeks later produces a typical Arthus phenomenon (Boehmig¹²⁶). Dienes and Schoenheit¹²⁷ report that repeated injections of egg white and horse serum in tuberculous guinea pigs elicit reactions that cannot be distinguished from typical tuberculin-allergic reactions. Positive cutaneous reactions of tuberculous patients to the local introduction of horse serum, broth, B. coli vaccine, etc., were demonstrated by Dujardin and Decamps, Potter, Selter, and others.

The writers believe that the pathogenesis of infantile dermatitis likewise can be explained on the basis of metallurgy. Almost every eczematous infant gives a positive cutaneous reaction to egg white: this would seem to show that the fetus had been allergized *in utero*. Further support for this belief is derived from the fact that intra- or subcutaneous injections of egg white in these infants frequently cause anaphylactic symptoms. However, the fact that complete elimination of egg from the diet is rarely followed by much clinical improvement seems to indicate the presence of allergic factors aside from the hypersensitiveness to egg white. Such allergic factors have been identified as exogenous substances (e.g., wool, silk) by Peck and Salomon¹²⁸ and Osborne and Walker,¹²⁹ and also as bacteria from intercurrent otitis or from pathologic intestinal flora (Urbach¹³⁰). The senior author set up the working hypothesis some years ago that such exogenous and endogenous allergens exert their influence on the basis of metallurgy.

Metallurgy readily explains how a specific allergy can be transformed into a polyvalent

¹²³ PARKER, J. T. *J. Immunol.* 9, 515, 1924

¹²⁴ SHELMIER, B.: *J.A.M.A.* 113, 1985, 1929

¹²⁵ FERRY, N. S. *ibid.* 87: 241, 1926.

¹²⁶ BOEHMIG, R. *Zentralbl. f. allg. Path. u. path. Anat.* 43 (suppl.): 130, 1937

¹²⁷ DIENES, L., and SCHOENHEIT, E. W. *Am. Rev. Tuberc.* 29: 92, 1929; *J. Immunol.* 19, 41, 1930

¹²⁸ PECK, S. M., and SALOMON, G. *Am. J. Dis. Child.* 46, 1308, 1933

¹²⁹ OSBORNE, E. D., and WALKER, H. L. *Arch. Dermat. & Syph.* 38, 511, 1938

¹³⁰ URBACH, E. *Wien. klin. Wchnschr.* 45, 1225, 1932

metaspecific allergy and how this in time can develop into a state of nonspecific hypersensitivity known as nonallergic pathergy. An example will illustrate this. A monovalent poison ivy dermatitis of the hands of a trained nurse first becomes metallergic that is certain agents such as bichloride of mercury and phenol cause a flare up of the dermatitis on the working hypothesis of a metantigen antibody reaction. If the skin condition persists the tissues will undergo a decrease in tolerance to nonspecific agents—i.e. all manner of nonspecific irritants (water soap friction etc.) will be capable of maintaining the existence of the dermatitis. This is the phase of nonallergic hypersensitiveness or nonallergic pathergy.

Thus in a system of allergic reactions metalergy stands between specific allergy and non-specific pathergy. Parallergy on the other hand cannot develop from allergy into the state of pathergy since the clinical manifestations elicited by the parallerger are entirely different from those elicited by the first antigen.

Metallergic Hypo and Insensitiveness

An excellent example of how cutaneous hyposenitization to one antigen can cause diminished reactivity to another antigen on the basis of metallergy was given by Higgin botham¹⁴. Daily subcutaneous injection of tuberculin into sensitized animals to the point abolishing the reaction to tubercle bacilli resulted simultaneously in a decrease of reactivity to other bacterial antigens such as *Bacillus coli* and *Staphylococcus aureus*.

Metallergic hyposenitiveness may also influence the reactivity to other infectious diseases. Thus the animal experiments of Bieling and Oelrichs¹⁵ have shown that the preinjection of lepra bacilli may definitely suppress the development of a subsequent virulent infection with tuberculosis. (This result depends of course upon certain time relationships and upon certain experimental conditions. As these authors pointed out under other conditions the opposite result is achieved that is a state of metallergic hypersensitiveness.)

Similar observations have been made in human beings. Calmette reports that among children vaccinated with BCG (Calmette Guerni bacillus) there is generally a much lower mortality rate from all causes than among children who have not been so inoculated and that this is attributable to the fact that the vaccinated children possess greater resistance to other infections. Likewise allergists are well acquainted with the fact that during hyposenitization therapy (e.g. with pollen) there is evidence of considerably reduced reactivity to other allergens.

The concept of metallergy is of notable theoretic as well as practical significance. This concept enables us to understand many hitherto inexplicable specific effects of apparently nonspecific factors. Thus for example it is commonly observed that cases of apparently monovalent allergic conditions (asthma rhinopathy dermatitis urticaria etc.) will sometimes react with specific manifestations to agents other than the specific allergen.

It would be unwise however to go so far as to speak of metallergy in a case of asthma or of dermatitis that reacts to all novae. Such a condition is more properly to be considered as the result of an increased nonspecific reactivity on the part of the given organ—that is nonallergic pathergy.

Furthermore the concept of metallergy facilitates our understanding of some types of so-called nonspecific therapy of allergic diseases. We are now able to understand the success of treatment by means of tuberculin and of peptone injections in specific asthma and other allergic conditions and to interpret these results as metantigen antibody reactions that induce the organism to increase its production of specific antibodies. We therefore prefer the designation of *metaspecific hypo-sensitization* to that of nonspecific hyposenitization for this form of anti-allergic treatment.

D. NOALLERGIC PATHERGY (PATHERGY IN THE STRICT SENSE)

In accordance with the definition given above nonallergic pathergy (known in brief as pathergy) embraces every hyper hypo-

or insensitiveness in which, at least at present, the antigen-antibody mechanism cannot be demonstrated, or in which, in the course of time, the specificity of the hypersensitiveness is lost and replaced by a nonspecific hypersensitiveness.

It is obvious that some diseases now included in the group of nonallergic pathergy may perhaps in the near future be considered as belonging to the allergic, parallergic, or metal-
lergic pathergies. For our understanding of these diseases is constantly progressing, as is also the development of technics for demonstrating the presence of antibodies, thus enabling us to recognize the antigen-antibody reaction.

1. NONALLERGIC HYPERSENSITIVENESS

To this group belong many cases of hypersensitiveness to actinic, thermal, mechanical, or chemical agents, such as diseases caused by light, urticarias due to heat, cold, or pressure, and certain contact dermatitides: these are instances of specific hypersensitiveness in which the antigen-antibody mechanism cannot be demonstrated, at least with existing methods.

A second and especially important group is represented by those originally specific allergies and metallergies that, for any number of reasons, lose their mono- or polyspecificity and enter the category of nonspecific hypersensitiveness. This may be exemplified by a case of specific horse asthma that reacts, after a while, to all manner of incitants, such as dust, wind, cold, and emotional upsets, or by a case of specific arsphenamine dermatitis of long standing, in which the basis of hypersensitiveness becomes broadened to such an extent that the skin also reacts with inflammation to water, soap, or friction.

Certain more uncommon phenomena should be included here.

As previously mentioned, von Behring described a specific toxin hypersensitiveness in animals. He found that in the course of treatment with essentially harmless doses of diphtheria and tetanus toxin, many animals reacted with symptoms characteristic for each type of toxin. Similar states of hypersensitiveness have occasionally been observed in human beings—for example, tachycardia due

to minute doses of belladonna; ringing in the ears and even deafness due to small doses of quinine; palpitation after drinking coffee; untoward reactions after moderate indulgence in nicotine or alcohol. All these are symptoms that are entirely dependent upon the nature of the causative substance—i.e., real intoxication brought on by extraordinarily small doses of the toxin or poison. This poison hypersensitiveness occurs in human beings and in animals and cannot be passively transferred to normal individuals by blood serum.

Tuft¹² employs the term "intolerance" for these symptoms, to indicate a quantitative difference in the physiologic response to a substance, whereas an allergic response is qualitatively different in character.

Finally, in our present state of knowledge, the local Schwartzman phenomenon and the general Sanarelli-Schwartzman phenomenon should be included among the nonallergic pathergies. Both consist of a toxin hypersensitiveness, based on an acquired altered reactivity of the organism.

The local Schwartzman phenomenon, first described in 1928, denotes the following experimental observations. An animal is prepared by one intracutaneous injection of a bacteria-free filtrate (e.g., of a typhoid bacillus culture). When the same filtrate is given intravenously twenty-four hours later, a hemorrhagic necrosis develops at the skin site originally injected, while intracutaneous or subcutaneous reinjection of the filtrate in the original injection site has no effect. Only those substances can be used for preparing the local skin site that have the capacity to produce an inflammatory swelling persisting for at least twenty-four hours. Culture filtrates containing endotoxins have proved to be particularly suited for this purpose. However, Schwartzman¹³ stresses the point that proper skin preparation does not require toxic damage to the tissue, but merely "a functional disturbance in the tissue cells, bringing about a transient state of vulnerability."

It is not necessary that the substances employed for preparing the skin and those injected intravenously to provoke the reaction

¹² Tuft, L. Clinical Allergy. Philadelphia: Saunders, 1937.

¹³ Schwartzman, G. Phenomenon of Local Tissue Reactivity. New York: Hoeber, 1935.

be identical, nor do they even have to be bacterial filtrates. The phenomenon can be evoked by an intravenous injection of a solution of agar or of starch after the skin has been prepared by colon bacilli filtrate. The reaction can also be elicited by intravenous injection of serum precipitates prepared by mixing foreign serum or egg white with homologous antiserum—even when bacterial filtrates have been used in the preparatory skin injections. It is also noteworthy that the provoking agents may include not only the precipitates formed in the course of an antigen-antibody reaction *in vitro*, but also the product arising from the union of antigen and antibody *in vivo*. Thus, if a rabbit is sensitized to horse serum, and is given intracutaneous injections of this serum three weeks later, it will show local allergic reactions. If, twenty-four hours later, horse serum is injected intravenously, hemorrhages will promptly appear in these sites and will later become necrotic (Albus and Schwartz). As shown by Aplitz¹⁴⁴ and confirmed by Horster and Mueller, a picture corresponding to the Schwartzman phenomenon can be produced by giving sensitized guinea pigs (e.g., to horse serum) intracutaneous injections of homologous serum (guinea pig serum), followed twenty-four hours later by an intravenous injection of the same serum. Plaut¹⁴⁵ demonstrated that even partial antigens (haptens) can produce the same results when combined with homologous antiserum. Finally, Bock has shown that the preparation for this reaction can also be achieved by epicutaneous application alone.

Gerber and Gross¹⁴⁶ have utilized the Schwartzman phenomenon to clarify certain aspects of human hypersensitivity to the sulfonamides. Rabbits were sensitized with sulfonamide azoproteins and then prepared by the intracutaneous injection of meningococcus filtrate. The phenomenon could be elicited twenty-four hours later by an intravenous injection of the homologous conjugate, the homologous protein, or a heterologous protein conjugated with a related sulfonamide, but not by the drug alone.

According to Gerber, the histologic changes occurring in the course of the Schwartzman reaction include severe capillary dilatation and engorgement of blood vessels, profuse hemorrhage, venous thrombosis, and perivascular collars of leucocytes with infiltration of the vessel walls. The walls of many of the small arteries are hyalinized.

Aside from symptoms of local tissue reactivity, there is also—as first shown by Sanarelli¹⁴⁷ in 1924—a *generalized tissue reactivity*. This is evidenced, for example, in a severe hemorrhagic diathesis in rabbits receiving intravenous injections, at twenty-four hour intervals, of doses of bacterial filtrates that in themselves generally do not produce reactions. Such generalized manifestations in human beings are very rare, a pertinent case following repeated injections of typhoid vaccine has been reported.¹⁴⁸ Since this special observation was first made by Sanarelli, and later studied by Schwartzman, it is often called the Sanarelli-Schwartzman phenomenon. The histologic changes seen in experimental animals include, in addition to the marked extravasations of blood, fibrin thrombi in the veins of the liver, spleen, pancreas and lungs, as well as arterial necrosis in the kidneys, adrenals, and bone marrow. Along with fibrin thrombi in the glomerular capillaries of the kidneys, there is extensive necrosis of the tubules and glomeruli. As a result of the vascular lesions, focal necrosis is observed in the malpighian corpuscles of the spleen, in the lobules of the liver, and in the myocardium.

Schwartzman advanced the following reasons for not identifying the phenomenon described by him with the Arthus phenomenon or with anaphylaxis. (1) The nonspecific local skin reactivity (Schwartzman phenomenon) requires an incubation period of about four to twelve hours and cannot be elicited after a lapse of 120 hours, while the incubation period for anaphylaxis is about ten days and the state of sensitiveness lasts for months or even years. (2) This local skin reactivity is not specific with regard to the relationship be-

¹⁴⁴ APLITZ K. *J. Immunol.* 29: 265, 1935.

¹⁴⁵ PLAUT F. *Ztschr. f. Immunitätsforschung exper. Therap.* 83: 490, 1934.

¹⁴⁶ GERBER I. E. and GROSS M. *J. Immunol.* 45: 103, 1944.

¹⁴⁷ SANARELLI G. *Les Entéropathies microbennes*. Paris, Masson, 1926.

¹⁴⁸ URBACH E., GOLDBURGH H. L. and GOTTLEB P. M. *Ann. Int. Med.* 29: 989, 1944.

tween the preparatory and the provocative factor, while anaphylaxis is highly specific. (3) The provocative factor for the Schwartzman phenomenon may even be nonantigenic substances such as agar-agar and starch. (4) The Schwartzman phenomenon can be elicited even in an animal rendered anti-anaphylactic by shock. (5) The local skin reactivity cannot be transferred passively by methods that are entirely satisfactory for transferring anaphylaxis passively, nor is specific desensitization possible. (6) While the Arthus phenomenon is elicited by the sub-

In human subjects as well, one must also differentiate between the local and the generalized forms. Harkavy and Romanoff¹¹⁹ observed three cases of local necrotic-hemorrhagic skin lesions (Fig. 4). Urbach and Goldburgh¹²⁰ described a severe hemorrhagic-necrotic reaction following the administration of 0.000002 mg. of tuberculin P.P.D., which may be regarded as representing the Schwartzman phenomenon (Figs. 5-8). There are also in the literature several cases reported as Arthus phenomenon following toxin-antitoxin injections that should properly be con-



FIG. 4 SCHWARTZMAN PHENOMENON. NECROSIS IN RIGHT THIGH

(Courtesy, J. Harkavy and A. Romanoff and *Journal of Allergy*)

cutaneous route, it is essential for the production of the Schwartzman phenomenon that the provocative dose be given intravenously. (7) Histologically, there are clear-cut differences: in the Schwartzman phenomenon there is an intense hemorrhage into the surrounding tissues, whereas such a condition is seen only exceptionally in the Arthus phenomenon.

The criteria that must be fulfilled in order to classify a hemorrhagic-necrotic lesion in man as a local Schwartzman phenomenon are: (1) the presence of a preparatory factor, usually originating from a focal bacterial infection such as sinus disease, or fungous infection; (2) the presence of a provocative factor, consisting of parenterally introduced bacterial antigens or toxins, or of products derived from the interaction of injected protein antigens with their corresponding antibodies.

considered as examples of the Schwartzman phenomenon (see p. 89).

Moreover, Sanarelli¹²¹ attempted to explain on this basis the pathogenesis and clinical picture of common acute diseases characterized by hemorrhage and necrosis (e.g., acute appendicitis). He was able to produce appendicitis experimentally in rabbits by first sensitizing the wall of the appendix with an injection of staphylococcus vaccine and then injecting *Bacillus pyocyaneus* filtrate intravenously. He is of the opinion that these acute conditions may depend upon a local sensitiveness of the tissue, which flares as a

¹¹⁹ HARKAVY, J., and ROMANOFF, A. *J. Allergy* 10: 66, 1939.

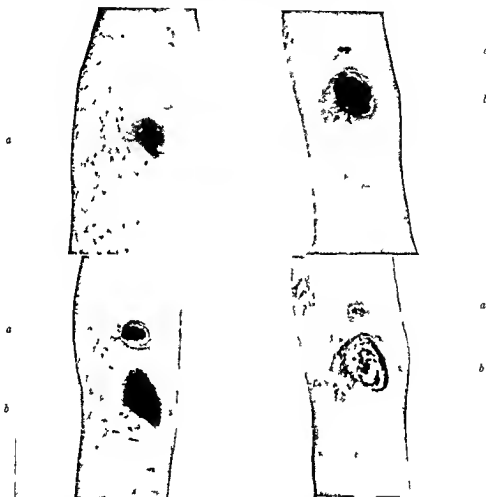
¹²⁰ URBACH, E., and GOLDBURGH, H. L. *Am. Rev. Tuberc.* 46: 418, 1942.

¹²¹ SANARELLI, G. *J.A.M.A.* 107: 1325, 1936.

result of the presence of toxic substances circulating in the blood

In human beings an equivalent of the generalized form of the Sanarelli Schwartzman phenomenon may perhaps be seen in the sud-

death following intravenous typhoid vaccine therapy reported by Urbach Goldburgh and Gottlieb.⁸ Love and Driscoll⁹ have recently confirmed this observation with a similar case



FIGS 5-8

SUCCESSIVE STAGES OF SCHWARTZMAN PHENOMENON PRODUCED BY TUBERCULIN P.P.D. GIVEN INTRACUTANEOUSLY

a — first test dose (0.00002 mg of P.P.D.) *b* — one tenth of first test dose (0.000002 mg)

FIG 5 (*upper left*) (*a*) After three days hemorrhagic necrosis

FIG 6 (*lower left*) (*a*) After eight days demarcation of necrosis (*b*) after thirty hours hemorrhagic reaction without necrosis

FIG 7 (*upper right*) (*a*) After twenty seven days very slow healing (*b*) after twenty days necrosis before separation of slough

FIG 8 (*lower right*) (*a*) After twenty nine days still not healing (*b*) after twenty days appearance following separation of slough

den hemorrhages into the exantheams in cases of measles or scarlet fever and into the vaccinal area after a first vaccination in the vaccinal exanthem after revaccination in anaphylactoid purpura etc. To this group belongs in all probability an instance of sudden

The examples presented as local and generalized Sanarelli Schwartzman phenomena in human beings seem justifiable since they

largely correspond with the clinical pictures described in experimental animals. The question arises, however, whether this phenomenon offers a satisfactory explanation for the reactivation of latent foci of infection by totally unrelated antigens. For instance, a patient with a latent sinus infection may suffer an exacerbation of his condition following exposure to a pollen to which he is sensitive. Harkavy and Romanoff¹¹⁹ offer the explanation that in such a case one may assume the formation of an antigen-antibody complex composed of the pollen and the pre-existing antibodies, which acts as a provocative factor in reactivating the infection. According to the definition given above (p. 28), we are rather inclined to consider this type of flare as metallergic in character.

The mechanism of the Sanarelli-Schwartzman phenomenon is not as yet known. It is certainly connected with the presence of soluble bacterial toxins. According to Gratia and Linz, it is a *hétéro-allergie hémorragique*—an opinion that Sanarelli and Schwartzman reject, for they do not admit any relationship of the phenomenon to allergy. This view is probably correct. Inasmuch as it apparently represents a nonspecific reaction, we have included it, at least for the present, in the group of nonallergic pathergies. Certain facts are evident, however, that might be interpreted as an increased specific tolerance and even specific immunity (e.g., neutralization of the preparatory or of the provocative substance by means of Schwartzman-immune horse serum, negative Schwartzman phenomenon in skin locally immunized by compresses soaked with culture filtrates, as reported by Stohlyhwo¹²²). Future studies will determine whether or not this is some special form of hetero-allergy.

2. NONALLERGIC HYPO- AND INSENSITIVENESS

It has long been known that a state of hypo- or insensitiveness of the skin and mucosa can be achieved by nonspecific methods consisting of repeated mechanical, thermal, or chemical stimuli. J. Jadassohn and his collaborators,

also Duke, Lewis and Grant, and others have made exhaustive investigations along these lines, and have shown that the skin can become habituated to such stimuli without evidencing a macroscopically detectable dermatitis, and that the process is a nonspecific one. This tolerance or adaptation (also called "hardening") to external chemical and physical agents is apparently based on a state of diminished reactivity.

The phenomenon of increased resistance to poison also belongs to the group of nonallergic hyposensitiveness. It was first reported by C. Richet, and exhaustive investigation of the fact was made by Schnabel, that it is possible to render bacteria resistant to certain chemicals that are otherwise bactericidal. This is achieved by culturing them in filtrates of strains of the same organisms that have been previously habituated to these substances (e.g., bichloride of mercury, optochin). Also included in this category is tolerance or habituation to chemical poisons (e.g., human habituation to poisons such as arsenic, alcohol, and alkaloids).

An additional example of nonallergic hypo- and insensitiveness is presented by the state of innate immunity, or preferably natural resistance. This, in turn, is to be divided into natural resistance to bacteria and to toxins. The term *natural bacterial resistance* expresses the well known fact that certain animals and certain races of man and even particular individuals are immune to given diseases naturally or under natural conditions.

In animals, the *natural resistance to toxins* may also be absolute or relative. Thus, the pig, the porcupine, and other species are totally insensitive to snake venom, while the hen and all cold-blooded animals are affected only by large doses of tetanus toxin. Resistance to bacterial toxins does not parallel resistance to the bacteria that produce the toxins. We do not, as yet, possess any clear understanding of the mechanism that is responsible for protection against these toxins. It may be in part the failure of the toxin to unite with the body cells and in part the capacity of the serum of the resistant animal to neutralize the toxin.

¹²² Stohlyhwo, N., Compt. rend. Soc. de biol. 130 31, 1939

MECHANISM OF ALLERGY

THE EXACT mechanism of the allergic diseases is unknown. There are numerous theories of which only the most important will be discussed here.

However, it would be well to consider first a significant question. Is allergy, *per se*, a disease, or is it merely an expression of a biologic reaction? Vaughan,²¹ Rackemann,²⁰ and Kahn¹⁵³ are of the opinion that hypersensitivity—or allergy—is merely a pathologic exaggeration of a normal physiologic response. Doerr⁹ had already pointed out that every individual possesses the capacity for being sensitized, that this process represents a normal defense mechanism, and that it is only the degree of sensitization that determines whether or not the ensuing picture is that of a clinical allergy. Tuft¹⁴² and Ratner stressed the growing conviction that, except for the allergic individual's specific hypersensitivity, he is in no way constitutionally different from a nonallergic individual, that the allergic subject is no more liable to sensitization to other allergens than a normal individual, and that he does not react to immunizing agents any more intensively than does a normal person.

The present writers hold, in agreement with Vaughan, that everyone is potentially allergic. The allergic state in humans generally becomes manifest, however, as a result of the interaction of various factors, namely, in individual heredity and constitution, various predisposing and contributory influences, and the allergenic nature of the responsible substances as well as the degree of exposure to them. These component factors need not be of equal importance. Thus, for one, the element of constitutional predisposition is not a necessary requisite. Furthermore, auxiliary factors that usually play so great a rôle in the pathogenesis of allergy have no importance when the allergens are especially potent. In other words, the factor of predisposition can be compensated for, in a given case, by

the factor of the exposure (Doerr). Further details will be given in the section on allergization.

ORIGIN AND NATURE OF ALLERGY

The view is now generally accepted that the mechanism of allergic phenomena is based on an antigen-antibody reaction taking place in the cells or tissues. This reaction has also been called the allergen reagin reaction. Furthermore, it has now been definitely established that neither the antigen (allergen) nor the antibody is, in itself, the noxious agent and that rather the union of the two initiates the clinical response. The proof of this consists of experiments that have shown that when an organism's supply of antibodies has been depleted, renewed exposure to the antigen does not elicit any pathologic changes.

For example, a rabbit that has been allergized with egg albumin responds to each subcutaneous injection of this protein with manifestations known as the Arthus phenomenon. However, when the rabbit's organism is flooded with great quantities of egg albumin, so that the antibodies are neutralized, it is impossible for some time to elicit allergic manifestations. For, if no antibodies are available, no antigen-antibody reaction can possibly be brought about (Opie).

However, another aspect of the question is still the subject of considerable controversy, namely, whether the union of the antigen and antibodies elicits in the blood or in the tissues certain chemical or physical processes that may be responsible for the allergic manifestations.

① Let us first consider the chemical theory. Richet was of the opinion that the union of antigen and antibodies produced a "poison"—the so called "anaphylatoxin." But this view has been abandoned, for we now know that the effect of the antibodies is to bind the antigen so thoroughly that it cannot continue to react with additional antibodies. Thus, Dale and Kellaway observed that the isolated sensitized

guinea pig uterus failed to contract when the bath contained sufficient free antibodies to counteract the added antigen. The antibody content of the solution was quantitatively controlled by the addition of appropriate amounts of homologous antiserum. If the antigen-antibody reaction, which under these conditions took place outside of the cells, had released a poisonous product, a contraction would have ensued. Actually such contractions occur only when the supply of antibodies is insufficient to bind the quantity of added antigen. The anaphylatoxin theory is further refuted by the fact that appropriate physical methods will effectively recover both reacting components of the antigen-antibody union in an unaltered state and capable of entering into a new reaction.

In the past few years, considerable interest has been aroused by the histamine theory of Dale and Laidlaw, and later by Lewis' theory of the release of a histamine-like substance—designated as the H substance—in the course of the antigen-antibody reaction. These hypotheses found their main support in the fact that the intravenous administration of small amounts of histamine in animals produces manifestations closely resembling those of anaphylactic shock. We shall critically examine these theories elsewhere (p. 103), and shall merely state here that "histamine shock" lacks one important finding always present in anaphylactic shock, viz., prolonged coagulation time of the blood.

In the past few years, the question has frequently been raised whether the manifestations of allergy may not depend upon some peculiar response of the organism to substances like acetylcholine or sympathin, which are normal products of the tissues. For a better understanding of this theory, we refer to the more recent investigations of Loewi and Dale on the chemical mediators of nervous activity. These authors have shown that when the sympathetic nervous system is stimulated, adrenergic substances (epinephrine and sympathin) are secreted by the cells in which the sympathetic nerves have their endings, while on the other hand a cholinergic substance (acetylcholine) is released when the parasympathetic fibers (vagus) are stimulated. The terms cholinergia and adrenergia

are now in general use, signifying imbalance of autonomic nerve activity. Patients who have a tendency to develop asthma, dermatitis, vasomotor rhinitis, urticaria, and angioneurotic edema often demonstrate other features of cholinergia, such as excessive sweating, salivation, indigestion of the hyperacid type, spastic colon, and dermatographism. Adrenergic stimulants usually produce prompt but temporary relief from this group of cholinergic symptoms.

Several Freoch authors (Villaret, Vallery-Radot, and others) report investigations along these lines and are of the opinion that the allergic states may depend upon an excess of acetylcholine or on some disturbance in its normal breakdown by the choline esterase.

In an effort to correlate the viewpoints outlined above, Wittich¹²⁴ has advanced a working hypothesis which is diagrammatically illustrated in FIGURE 9. It should be pointed out that all the physiologic and allergic responses which are, for illustrative purposes, separately depicted, usually take place in a single "shock tissue."

Space does not permit more detailed consideration of these theories. Suffice it to say that experiments by Went,¹²⁵ Code,¹²⁶ and other investigators reveal the inadequacy of the concept that anaphylaxis is the result of a simple histamine intoxication. It is more likely that, in the course of the anaphylactic reaction, several biologically active substances of different types (histamine, choline, epinephrine, etc.) are released from the various tissues, affecting the chemical regulation of the autonomic nerves and of the autonomic effector organs. Hence we feel justified in assuming that histamine, acetylcholine, and similar substances are the result and not the causes of antigen-antibody reactions.

Doerr is the outstanding champion of the physical theory. He assumes that antigens and antibodies of high molecular weight react in the cell membrane and cannot penetrate into the cell; thus, physicochemical changes are brought about and these act as irritants to

¹²⁴ WITTICH, F. W. Physiologic and Immunologic Aspects of Allergy, presented at the 1944 Regional Course of the American College of Allergists.

¹²⁵ WENT, S. Third Internat. Cong. Microbiol., 1939, p. 765.

¹²⁶ CODE, C. F. Ann. Allergy 2: 457, 1944.

the cells. According to Bronfenbrenner, the union between antibody and antigen serves to disturb the delicate adjustment of the colloidal conditions existing in the blood, as well as at the surfaces of the tissue cells. He believes that this results from activation of serum trypsin with subsequent autodigestion of the serum, and a resultant reaction to the trypsin and/or the products of its action. Widal looks upon anaphylactic shock as representing a disturbance of the colloidal

tigen in the given case, but almost exclusively upon the site of the cellular antibody. Although it is known that almost every tissue of the animal organism is capable of producing antibodies, it is also true that certain structures are to be regarded as being the principal shock tissues.

Knowledge of the tissues in which the antigen-antibody reaction takes place in the various allergic diseases is not only of theoretic interest but also of considerable practical

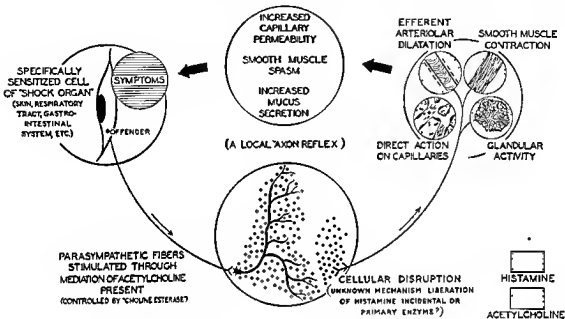


FIG. 9 SCHEMA OF POSSIBLE MECHANISM OF ALLERGY (after Wittich¹⁵¹)

balance. He and his school see fit to designate the changes of the colloid in the blood observed during attacks as the "hemoclastic crisis," and those in the tissues as "colloidal-clasia." Lumiere, on the contrary, explains the nature of anaphylactic phenomena on the basis of invisible flocculation occurring in the blood stream of allergic individuals as a result of the encounter between antigen and serum antibody. In support of his views, he cites the fact that *in vitro* flocculation follows the admixture of the antigen with the serum of allergic individuals.

B PRIMARY SHOCK TISSUE

The precise clinical picture of an allergic disease will scarcely ever depend upon the an-

importance. Obviously, more satisfactory and more reliable results will be obtained when tests are made directly on the shock organ in question. The same will be true, of course, with regard to therapy. Table 4 presents a summary of the principal shock tissues involved in the more important allergic diseases.

As the senior author¹⁵⁷ has shown, the differentiation between an epidermal (or epimucous) and a vascular hypersensitiveness can be made by means of epinephrine or alypin iontophoresis. This has been confirmed by Widder¹⁵⁸. The method is as follows. The allergen is applied to skin or

¹⁵⁷ URBACH, E., and WIEDMANN, A. Arch. f. Dermat. u. Syph. 136: 593, 1928.

¹⁵⁸ WIDDER, M. Dermat. Wchnschr. 109: 1353, 1939.

mucosa previously made ischemic by the iontophoresis of a 1 per cent epinephrine solution. This renders the contracted blood vessels of the cutis or mucosa incapable of

TABLE 4—*Clinical Manifestations of Human Allergy as Determined by the Primary Shock Tissue*

Primary Shock Tissue	Clinical Manifestations
Epidermis	allergic contact dermatitis
Blood vessels of cutis	neurodermatitis, infantile dermatitis, urticaria papular urticaria prurigo angioneurotic edema
Blood vessels of sub-cutis	
Nasal epimucosa*	allergic rhinopathy of exogenous origin, hay fever
Blood vessels of nasal mucosa	allergic rhinopathy of endogenous origin (alimentary, hematogenous)
Bronchial epimucosa	allergic asthma of exogenous origin, allergic bronchitis
Blood vessels or musculature of bronchi	allergic asthma of endogenous origin (infectious, alimentary, hematogenous etc.)
Gastric epimucosa	vomiting, especially of cyclic type
Intestinal epimucosa	diarrhea, mucous colitis
Smooth muscle of urinary bladder	vesical spasm of endogenous origin
Smooth muscle of gallbladder	gallbladder spasm of endogenous origin
Peripheral blood vessels	periarthritis nodosa, nodule crises, Schoenlein's and Henoch's purpura
Cerebral blood vessels	allergic migraine, allergic epilepsy
Central nervous system	paroxysmal tachycardia paroxysmal profuse sweating extreme fall of blood pressure
Synovia of joints	paroxysmal hyarthrosis

* The term epimucosa, corresponding to the term epidermis, is used to designate the superficial layers of the mucous membranes.

participating in the allergic reaction. Consequently, if no objective manifestations or subjective symptoms are observed, the case is to be considered as one of vascular hypersensitiveness. On the other hand, if reactions appear, they are to be considered as manifestations of epidermal or epimucous allergy. As a check, iontophoresis with 20 per cent alypin (a topical anesthetic) is carried out

until tactile sensation is abolished. If epidermal application (e.g., of egg white) now elicits an urticarial response, the case is one of vascular hypersensitiveness; if, however, there is no such response, it may be considered as an epithelial allergy. Likewise, if the insufflation of pollen on a nasal mucosa similarly anesthetized with alypin does not result in itching or rhinorrhea within two hours, the same conclusion must be drawn.

Another noteworthy fact is that the portal of entry of the allergen need not be identical with its principal site of action, generally called the shock tissue. For example, when the ingestion of acetylsalicylic acid is followed within a few hours by an attack of rhinorrhea, the portal of entry is the intestinal mucosa, while the primary shock tissue is the nasal mucosa. To express this more clearly, we recommend adding the qualifiers "primary" and "secondary" to the designations "epidermal," "vascular," etc. "Primary" is intended to show that the allergen acts *directly* on the epidermis, the vessels of the cutis, or other tissue. The qualifier "secondary," on the other hand, is intended to designate the situation in which the agent first comes into contact with the stomach or intestinal mucosa, for example, while it reaches the skin, where manifestations are elicited, only *secondarily* (e.g., cases of neurodermatitis or urticaria caused by foods or drugs). It is of major therapeutic importance to know, in a given case, whether or not the portal of entry is identical with the allergen's principal site of action. Thus, a course of cutaneous hypsensitization would seem promising in a case of neurodermatitis (e.g., due to hypersensitiveness to transepidermal penetration of horse dander) in which the blood vessels of the cutis represent the portal of entry. Such an attempt at cutaneous hypsensitization would be of little avail, however, in a case of allergic skin disease with primary intestinal entry of the allergen and only secondary involvement of the cutaneous blood vessels. In such a case, administration of the allergen by mouth might very well be useful. Templeton⁵⁹ has recently stressed the significance of the portal of entry in pointing out that in some patients the same allergen (food, drug,

⁵⁹ Templeton, H. J. J.A.M.A. 127: 908, 1915

plant substance etc.) may reach the sensitized skin either by direct contact or by way of the blood stream after absorption giving rise to the same clinical manifestations in either case.

In this connection one more question must be considered namely why in a given case one organ becomes hypersensitive and another organ does not. The localization of the allergy is dependent upon various conditions. The experiments of Roth and Szauder are most enlightening. They showed that in the allergized animal the localization is dependent upon the portal of entry. For if the allergen is injected for example into the carotid artery in the direction of the brain cerebral symptoms will develop (tonic clonic convulsions followed by loss of consciousness), while injection into the jugular vein will be followed by pulmonary manifestations and injection into the portal vein will induce disturbances of liver function. It is of course much easier to understand why an organ becomes hypersensitive when its tissues come directly into contact with the allergen—i.e. when it also serves as portal of entry (as does the nasal mucosa in hay fever the bronchial mucosa in asthma etc.) But even in these instances the matter is not as simple as might at first appear.

Let us consider for example the elicitation of rhinopathy by a food or of asthma by a drug. One might of course attach responsibility to a congenital or acquired predisposition of the organ involved. But the experimental investigations of Klinge as well as of Riehm and his school are more illuminating and more convincing. These authors began with the so called Auer phenomenon (injection of xylool elicits no reaction in normal animals but severe local skin inflammation and necrosis in allergic animals) and they succeeded in showing that all manner of non-specific irritations can influence the localization of the hypersensitivity. The allergic tissue injury can be selectively directed to any chosen organ of an allergized animal provided thermal mechanical or nonspecific bacterial stimuli are employed to produce local circulatory disturbances including hyperemia or stasis and are followed by intravenous injections of small quantities of antigen. According to these authors a local increase of the circulating antigen ensues under such

circumstances resulting in a reaction with the cellular antibodies. The same general principle has been employed by others to localize the allergic response to the brain the joints the eye and other organs.

But all this does not suffice to account for the choice of organ in all cases. To explain it Nathan Masugi and others have set up the following theory on the basis of animal experimentation. There are antibodies that are organ specific (i.e. directed against a particular type of tissue) and these play a determining rôle in this regard. By employing serums that contained such antibodies or by producing auto antibodies to a given organ these authors succeeded with repeated administration of antigen in localizing the tissue injury in a given organ.

Despite all these interesting and ingenious experiments we must confess that we are still totally ignorant as to why a vascular cutaneous allergy will express itself in one case as an urticaria in a second case as a neurodermatitis and in a third case as a prurigo.

C ALLERGIZATION

The term *allergization* designates acquisition of the capacity to become hypersensitive to one or more substances as a result of the active production or passive administration of specific antibodies.

Allergization is thus a well defined subdivision of *sensitization*. By the latter term we mean a pathologic increase in the state of sensitivity of the various tissues to all manner of stimuli whether or not the hypersensitivity is based on an antigen antibody mechanism. These two terms are therefore not identical and should not be loosely employed as synonymous as is so often done.

In order to designate clearly the fact that in a given case of hypersensitivity the antigen antibody mechanism either is not demonstrable by any known method or has been lost by reason of nonspecific broadening of the basis of reaction the term *pathergization* is recommended.

When an organism is allergic other agents may be capable of eliciting manifestations of hypersensitivity without the intervention of specific antibodies. This mechanism is referred to as *heteroallergization*. This is subdivided into *parallelization* when the new

symptoms are different from the original ones, and *metallergization* when similar clinical pictures are elicited in both instances

Recent investigations have shown that all individuals are potentially capable of developing allergy. The question naturally arises as to why, under these conditions, only relatively few individuals become hypersensitive to certain allergens. The answer—according to present knowledge—lies in the fact that the capacity to become allergic depends upon the combination of necessary predisposing factors, as well as upon the nature of the excitant acting as allergen. The significance of the predisposing factors, such as heredity, constitution, endocrine glands, sympathetic nervous system, infections, intoxication, gastrointestinal resorption, hepatic dysfunction, abnormalities in any of the physical or chemical barriers of the skin, meteorologic and geographic conditions, and psychosomatic influences, will be discussed in a separate chapter. The capacity of a substance to become a potent antigen depends upon various factors, including the nature of the exciting substance, the amount and concentration of the antigen to which the individual is exposed, the duration and mode of the exposure, the extent of the exposed surface, and the like.

The capacity to become allergized is therefore the resultant of exogenous and endogenous stimuli (factor of exposure) plus the predisposing factors, particularly the individual constitution. Concerning the reciprocal relationship between exposure and the various predisposing factors, it may be said that the greater the influence of the excitant, the less important are the factors of predisposition, while on the other hand, in cases involving only weakly effective agents, it seems likely that only constitutionally predisposed individuals will become allergized.

Allergization may be either *active* or *passive*. In cases of active allergization, the organism is directly exposed to the allergen, with the result that antibodies are produced. The term passive allergization designates the transference of hypersensitiveness by means of antibody-containing serum from an actively allergized animal or human being, either generally or to a local skin or mucous membrane site. Thus, experimental passive allergization

has its clinical analogue in an attack of asthma that developed in a patient driving behind horses after receiving a blood transfusion from a donor who was sensitive to horse serum (Ramirez) or in the occurrence of rhinopathy in a child following contact with rabbits, after the child had received an injection of serum from an asthmatic patient allergic to rabbit hair (Frugoni). This mechanism is also the basis of the methods employed for the local passive transfer of hypersensitiveness (Prausnitz-Kuestner, Urbach-Koenigstein reactions).

It is as yet hardly possible to give a definite answer to the question as to whether allergization affects only a certain tissue or organ, or the entire organism. In experimental animals, one almost always obtains a positive Schultz-Dale test with the excised uterus as an indication of general allergization in guinea pigs in which the inhalation of horse serum has induced bronchial hypersensitiveness (Undritz) or when intracutaneous injections of simple chemical compounds are followed by the appearance of an allergic dermatitis (Landsteiner). Salén is of the opinion that a state of universal allergization will explain why some allergens can at different times elicit allergic manifestations in different organs and tissues of one individual. He also believes this to be the explanation of the extraordinary variety of allergic symptoms seen in shock—a fact that would tend to indicate that numerous tissues have been allergized. On the other hand, numerous clinical observations would seem to signify that very frequently only a certain type of tissue (e.g., the bronchial mucosa or only the vascular system of the cutis) has been allergized; and this view receives even stronger confirmation from the fact that, in cases of fixed drug exanthems, only a very few and strictly localized skin sites react allergically.

An individual can become allergized at any time of life. Clarke and Leopold,⁶⁷ for example, reported the case of a seaman who developed hay fever only after being pensioned at the age of 72 years. The senior author has observed 8 men and 3 women who suffered their first attacks of asthma between the ages of 61 and 70 years. On the other hand, it is well known that particular allergic diseases are associated with certain periods of life—

as, for example, strophulus and cyclic vomiting during infancy and early childhood and prurigo, migraine, and dermatitis medicamentosa during adult life

As Black³²⁹ points out a great many patients and some physicians try to explain a recently developed allergy on the basis of some food which has been newly added to the diet or some new factor in the environment. More often they are found to be sensitive to food or environmental or other factors to which they have been exposed for years. In other words, it is the patient and not the diet or environment which has changed.

The duration of the allergic state varies from several weeks to many decades, depending upon the nature of the allergic disease. In cases of strophulus, urticaria, and allergic diarrhea, strict elimination of the agent responsible (especially if it is a food) can restore

latent period is usually between eight and eleven days. Under certain conditions however this same process may take months and even years.

The optimal allergizing dose of the preparatory allergen varies according to the nature of the substance, the species of the animal and the manner of administration (Table 5 will serve to demonstrate this). In principle it may be said that moderate amounts of antigen are more effective in sensitizing for laboratory experimentation than extremely small or very large quantities. For example guinea pigs that have been allergized with 1 cc of horse serum are subsequently more hypersensitive than guinea pigs that have received 0.1 cc. Zinsser believes that the relative ineffectiveness of amounts that are too large may be due to a persistence of the antigen in the circulation after antibodies have begun

TABLE 5—Optimal Doses of Allergens for Allergizing Guinea Pigs

Antigen	Subcutaneous Preparatory Dose (Cc)	Number of Allergic Injections	Optimum Latent Period after Last Previous Injection	Intravenous Shock Dose (Cc)
Horse serum	0.01–0.25	1	2–3 weeks	0.10–0.50
Egg white	0.001–0.1	1	3 weeks	0.01–0.10
Pollens	1.0 (3% pollen extract intraperitoneally)	3 at intervals of 7 days	3 weeks	0.5 (10% pollen extract)

the patient's tolerance of the allergen within two to three weeks. In hay fever, asthma, and dermatitis, however, conditions are quite different here the hypersensitiveness generally persists throughout life. We might mention the case, seen by us, of a hay fever patient who spent twenty years in the tropics and suffered no symptoms during all this time, in the summer after his return home, however, he presented his former manifestations of hay fever. Similar observations have been made in cases of asthma induced by horse, dog, or cat danders. Such patients may be entirely free from symptoms for years and yet react severely on a renewed exposure to the given animal.

The time required for allergization—that is to say, the period elapsing between the first exposure to the allergen and the first manifestation of an alteration in reactivity—depends upon numerous factors. In serum sickness and in all biologically similar disease, the

to form. As a consequence, there may be a certain degree of protracted hyposensitization. Furthermore, when the allergen is reinjected several days before allergization has taken place, the onset of the latter is deferred.

Several experiments may be mentioned here to illustrate how almost inconceivably minute doses may produce allergization. Wells¹⁰⁰ for example was able to achieve hypersensitiveness in a guinea pig by means of a single dose of 1/20,000,000 Gm of crystalized egg albumin. Doerr and Berger produced it with 0.0000004 Gm of horse serum euglobulin. Schwitzer¹⁰¹ found that sensitization to dinitrochlorobenzene in the guinea pig by the intracutaneous route requires between 2.5 and 1 gamma of this chemical. Such values are reminiscent of those found in vitamin, enzyme, and endocrine processes.

¹⁰⁰ WELLS, H. G. *Chemical Aspects of Immunology*, ed. 2. New York: Chemical Catalogue Co., 1929.

¹⁰¹ SCHWITZER, A. *Dermatologica* 85: 339, 1942.

They may be compared with the growth-promoting effect of biotin on yeast when present in a concentration of only 1 part in 400 billion, with the dilating effect of epinephrine on the pupil of the frog eye in a concentration of 1 in 20 million, and with the effect of thyroxin on the metamorphosis of the tadpole in a dilution of 1 to 5 billion.

Not only is it possible to induce allergization by proteins, as was formerly claimed, but the fact has now been established that carbohydrates, lipoids, and even inorganic chemicals can serve as antigens—or more accurately, as partial antigens or haptens.

A most important consequence of Landsteiner's¹⁰² hapten theory is that it enables us to understand how externally applied drugs and chemicals, or internally administered drugs, can become allergizing agents. For, when the application or contact with these substances occasions a slight local damage, sufficient to liberate some tissue protein, this protein assumes the character of an auxiliary antigen and can thus conjugate with the hapten—"drug," "chemical," etc.—forming a complete antigen. This mechanism may be clarified by the following case¹⁰³ of allergization of the buccal mucosa and skin to drugs taken during the course of a gangrenous herpes zoster.

A woman aged 52 presented herpes zoster associated with deep ulceration and a temperature of 103.8 F. Small doses of acetylsalicylic acid and amidopyrine were administered at this time. The patient had formerly tolerated these drugs. After six days, she presented diffuse dark bluish-violet areas of inflammation on the mucous membrane of the cheeks, gums, and lips, together with vesiculation. Two days later, the trunk and extremities showed a widespread reddish-violet eruption. After these manifestations had subsided, skin tests were made with acetylsalicylic acid and amidopyrine, with negative results. However, subsequent administration by mouth of 0.5 Gm of acetylsalicylic acid and two days later of 0.1 Gm of amidopyrine brought on a decided exacerbation of the mucous membrane and skin lesions, as well as a severe attack of pruritus. There were no signs of agranulocytosis.

This allergization of the organism is probably attributable to a linking of the two drugs with body protein altered as a result of the ulcerated

herpes and the high fever, thus forming a conjugate antigen. In order to express clearly the mechanism of this type of allergization, it should be referred to as *haptenization*.

Another mechanism of allergization might perhaps be found in the so-called *auto-allergization*. Together with Whitfield¹⁰⁴ and Barber,¹⁰⁵ we employ this term to designate manifestations of hypersensitiveness produced by substances of the body itself that have become foreign to the body. This subject will be discussed in some detail in the section on endogenous allergens (p. 118). Here we shall merely say that the concept involves the body's own protein, which has undergone alteration of its chemical structure as the result of some profound damage—e.g., metabolic abnormalities, incomplete protein digestion due to gastro-intestinal disease, functional endocrine disturbances, or some local trauma, scalding, or excessive exposure to sunlight. Such auto-allergization also seems to be the basic cause of the so-called auto-anaphylactic diseases of the eye and of the physical allergies that the French (Widal, Joltrain) significantly call *autocolloïdodase*.

Closely related to the mechanism of auto-allergization, but different from it in the nature of the antigens involved, are two other forms of *endogenous allergy*, viz., the endogenous bacterial and parasitic allergies. This entire problem will be considered in detail later (p. 136).

Allergization may take place from without or from within the organism. Likewise, the agent eliciting the allergic manifestations may reach the body by either route. Thus, four possibilities may be encountered, as illustrated in Table 6. In recent years it has often been observed that skin areas may be sensitized by the application of a sulfonamide ointment and a dermatitis follow the oral administration of the same sulfonamide at a later date. The following case (Gottlieb¹⁰⁶) illustrates epidermal allergization and intramuscular elicitation by penicillin:

A doctor, in opening penicillin ampules, inadvertently but repeatedly got some of the drug on his fingers. As a result he acquired a mild erythematopapular

¹⁰² LANDSTEINER, K. *The Specificity of Serological Reactions*. Springfield, Ill.: Thomas, 1930.

¹⁰³ UEBACH, E. *Zentralbl. f. Haut- u. Geschlechtskr.* 56 6, 1937.

¹⁰⁴ WHITFIELD, A. *Brit. J. Dermat.* 31: 331, 1927.

¹⁰⁵ BARBER, H. W. *Practitioner* 123: 279, 1932.

¹⁰⁶ GOTTLIEB, P. M. unpublished observation.

dermatitis of portions of the second and third fingers of each hand. This subsided promptly when he discontinued contact with the drug. About eleven months later he was given penicillin intramuscularly for the treatment of an infection and shortly after the second dose (about four hours after the initial injection) had an acute vesicular nearly bullous flare of the previously involved areas. The next day generalized urticaria and angioneurotic edema of the eyelids appeared. All lesions cleared promptly after treatment was discontinued.

Templeton¹⁵⁹ has recently re-emphasized the simultaneous existence of epidermal and dermal sensitization in the same patient. He points out that, although this problem is

TABLE 6—Routes of Allergization and of Elicitation of Allergic Phenomena

	Allergization Brought About	Clinical Manifestation Brought About
1	From without by sulfadiazine ointment	from without by repetition of sulfadiazine ointment
2	From without by sulfadiazine ointment	from within by orally administered sulfadiazine
3	From within by orally administered sulfadiazine	from within by repetition of orally administered sulfadiazine
4	From within by orally administered sulfadiazine	from without by sulfadiazine ointment

particularly important with respect to drugs, such combined allergization may also result from plants (particularly from *rhus* toxin or primrose), foods, and endogenous substances. Cooke⁶⁸ has concluded that in chronic dermatitis, it is immaterial both immunologically and clinically, whether the allergen reaches the skin from without, by contact, or from within (after absorption of inhaled, ingested, or injected substances, or of bacterial products from foci of infection).

In considering the various routes by which allergization can be effected, attention must be directed, first and foremost, to the skin and to the mucosa of various organs (conjunctiva, nose, bronchi, gastro-intestinal tract, gall-bladder, vagina, etc.), as well as to the

placenta. Here we wish to stress once again that the tissue through which the allergen enters the organism may, at this time, become allergized, though not necessarily. Let us consider two examples. (1) The portal of entry of the allergen is the intestinal mucous membrane, and the result is mucous colitis. (2) The portal of entry is again the intestinal mucous membrane, but the result is asthma or urticaria. Whether or not the shock tissue will be the same as the portal of entry probably depends in a given case upon various conditions, including predisposing factors, nature and quantity of the antigen, duration of the exposure, and extent of the exposed surface.

For obvious reasons the skin has been utilized for experimental allergization far more than other tissues, not only in the investigation of cutaneous allergies but also in the elucidation of many general basic problems. Allergization of the human skin may take place in the epidermis and/or in the cutis, and can be caused by nonprotein as well as by protein substances. We shall first consider epidermal allergization, and point out that foreign protein may be effective by the epidermal route. Thus, Hartoch and his associates report that injection of horse serum brought on a state of specific allergization that was at first local and then became generalized. Nestler, as well as C. Low, demonstrated that a dermatitis could be elicited in normal individuals by rubbing the intact skin with primrose leaves. The allergization is not restricted to the treated site, but extends to the entire skin surface.

Bloch's¹⁶⁷ exhaustive experimental investigations of the possibility of producing obligatory allergization by means of nonprotein substances opened up a new era of intensive work along these lines. As a result of these studies, we now possess a reasonably clear understanding of the mechanism of those types of "eczema" that are now called contact dermatitis.

Thus, Landsteiner,⁶⁹ Wedroff and Dolgoff,¹⁶⁸ Sulzberger and Baer,¹⁶⁹ Haxthausen,¹⁷⁰ and

¹⁶⁷ BLOCH B. and STEINER W. *Arch. f. Dermat. u. Syph.* 1:2 283 1926

¹⁶⁸ WEDROFF N. S. and DOLGOFF A. P. *ibid.* 1:7 647 1935

¹⁶⁹ SULZBERGER M. B. and BAER R. L. *J. Invest. Dermat.* 1 43 1938

¹⁷⁰ HAXTHAUSEN H. *Acta dermat. venerol.* 20 257 1939

others succeeded in allergizing the human skin to simple chemical compounds (e.g., nitrochloric benzenes), and other authors achieved allergization to neoparsphenamine, ursol, orthoform, phenylhydrazine, iodoform, urushiol, arnica, etc. All this seems to correspond with the clinical observations of Walthard¹⁷¹ that from 40 to 100 per cent of workers in the Swiss nickel industry developed nickel dermatitis after an incubation period of from fourteen to twenty-one days, and of Dore, Thomas, and Green¹⁷² that 50 per cent of those employed in a British plant manufacturing morphine acquired a persisting sensitivity to the products handled. These suggest a true allergization.

Aside from these methods of active allergization, it is also possible to allergize the human epidermis *passively*. This is accomplished by means of antibody-containing blister fluid (Urbach-Koenigstein technic, p. 150). The senior author¹⁷³ demonstrated this in the following experiment. The skin site of a normal subject was prepared by an intracutaneous injection of blister fluid from a patient allergic to primrose. The next day a primrose leaf, cut in the shape of a triangle, was placed on this site. Twenty-four hours later, a definite eczematous skin reaction was observed on the site (FIG. 40).

The animal epidermis likewise can be rendered hypersensitive to a great variety of protein and nonprotein substances. Pierret and Gernez,¹⁷⁴ for example, reported epidermal allergization by means of serum dressings. Bloch¹⁷⁵ succeeded in allergizing guinea pigs with eczematoid response by inunction with primin (crystallized primrose extract). Similar results have been achieved with poison ivy (Simon et al.; Ginsberg, Becker, and Becker); with *Rhus vernicifera* (Kobayashi); with primrose extracts and ragweed pollen (Brunsting and Bailey); with 10 per cent paraphenylenediamine (R. L. Mayer); with 5 per cent ammonium or potassium persulfate (Urbach; Zitzke); with nickel sulfate (Walthard; Stewart and Cormia); with phenylhydrazine (W. Jadassohn); with quinine (Land-

steiner and Chase). Straus¹⁷³ allergized rhesus monkeys to poison ivy by means of the patch test technic.

In addition to epidermal allergization, there is also another, somewhat less important type of skin allergization, viz., the *cutaneous* or *intracutaneous* form. For an allergen may gain admission through a break in the skin caused by chafing, tiny lacerations, alkalies, fat solvents, etc. It may also be the sequel of intracutaneous injections, as observed both in inadvertent clinical occurrences and in experimental investigations. Moreover, Dowdeswell¹⁷⁶ achieved generalized cutaneous allergization by the application of various pollen extracts or antigas-gangrene serum to denuded skin sites (produced by the application of phenol) in ten non-allergic subjects. Here, too, first a local and then a generalized state of allergization is produced by antigens of protein and nonprotein nature, in the latter case with the aid of auxiliary (carrier) substances.

Particularly efficient for the purpose of allergizing the skin is the so-called "depot method" of Lehner and Rajka,¹⁷⁷ in which the injections are repeatedly made into precisely the same skin site. By this means one can even allergize the skin to such haptens as tuberculin or trichophytin, the damaged skin protein acting as the carrier.

The fact that the allergization in all these cases is based on an antigen-antibody reaction is proved by the spontaneous flare of the sensitized skin sites after the expiration of the incubation period (usually nine to eleven days), by the reaction of the allergized sites upon renewed injection of the antigen, and by the appearance of a universal urticarial or morbilliform erythema following intracardiac administration of the antigen in animals (Frei; Bloch and Steiner-Wourisch).

The length of the incubation period required for allergization of the skin varies according to the allergen employed, the manner of administration (epidermal, intracutaneous), the species of animals, and similar factors. Usually the state of allergization becomes manifest after the second or third application or injection.

¹⁷¹ WALTHARD, B. *Schweiz med Wchnschr* 56: 603, 1926.

¹⁷² DORE, S. E., and THOMAS, E. W. P. *Brit J Dermat* 56: 177, 1944.

¹⁷³ URBACH, E. *Zentralbl f Haut- u Geschlechtskr* 39: 273, 1932.

¹⁷⁴ PIERRET, R., and GERNEZ. *Compt rend Soc de biol* 92: 795, 1925.

¹⁷⁵ STRAUS, H. W. *J Immunol* 32: 241, 1935.

¹⁷⁶ DOWDESWELL, R. M. *East African M J* 21: 11, 1944.

¹⁷⁷ LEHNER, E., and RAJKA, E. *Allergische Reaktionen der Haut*, Halle, Marhold, 1937.

tion of the allergen—i.e., after from ten to fifteen days

Finally, as to the mechanism by which an initially localized skin allergization becomes generalized, there are three possibilities (1) the allergen is carried by way of the blood and lymph so that all the cells become actively hypersensitive, (2) the allergen remains local but antibodies are transported from the site of formation by hematogenous and lymphogenous spread, (3) active allergization extends in the skin from one epithelial cell to another by way of the intercellular bridges in the stratum spinosum

There appears to be little agreement among the authors who have studied the subject Schreus Straus and Coca and Haxthausen all more or less favor the theory that the spread of allergization occurs by the epidermal route On the other hand the experimental investigations of Simon,¹⁷³ and of Landsteiner and Chase,¹⁷⁴ have decisively demonstrated that the extension is dependent upon the free circulation of the lymph When this circulation is prevented transportation of the causative material becomes impossible, with the result that the allergization cannot become generalized This difference of opinion is explained by the failure of the first group of investigators to interrupt the circulation in the deep lymphatics Therefore the continuity of the deep lymph channels of the skin is a prerequisite for the spread of cutaneous allergization

The mucous membranes, like the skin are susceptible of allergization either actively or passively to substances both of protein and nonprotein nature Anatomic differences might well explain the fact that the mucosae of the nose, bronchi, and gastro intestinal tract much more frequently present allergic manifestations than do the mucosae of the mouth, vagina, and urethra

Riehm¹⁸⁰ reported allergization by way of the conjunctiva

Simon and Rackemann¹⁸¹ succeeded in allergizing a human being via the nose with guinea pig serum, applied locally for about thirty

minutes and repeated three to six times at intervals of from three to fourteen days After a short time allergic symptoms began to manifest themselves in the form of a serous discharge sneezing and a stopped up feeling in the nose The fact that the allergization was generalized was proved by positive intracutaneous tests with this serum Petragiani¹⁸² reported similar results by means of nasal instillation of diluted foreign serum in guinea pigs Linch¹⁸³ allergized guinea pigs by insufflation of dry ragweed pollen into the nostrils, this was followed by local reactions resembling hay fever Sherman and his associates¹⁸⁴ achieved passive sensitization of the nasal mucosa by intramucosal injections of antibody containing serum

In contrast with the paucity of experimental work on the conjunctiva and nasal mucosa there is a rather extensive literature dealing with allergization of the bronchial mucosa We have discussed this question in some detail elsewhere (p. 46)

Bircher as well as Helmke succeeded in allergizing the mucosa of the mouth to prim rose

Let us now consider conditions in the various other portions of the gastro intestinal tract It should be stressed that although any food or drug may act as an antigen, in general this takes place relatively infrequently Allergization—as will be shown in detail elsewhere—therefore depends on certain quantitative and qualitative factors as regards both the administered substance and the absorptive capacity of the mucous membrane

We now know that the gastro intestinal tract especially in young children is permeable to food proteins in their unaltered state even if ingested in small amounts This can readily be demonstrated by serologic methods Moreover, Walzer¹⁸⁵ demonstrated by passive transfer that nutritional proteins are absorbed and appear in the blood of normal nonallergic individuals Ratner and Gruhl¹⁸⁶ are of the opinion that such normal absorption of nutritional protein may serve a useful purpose in

¹⁷³ SIMON F A J Immunol 30 275 1936

¹⁷⁴ LANDSTEINER K and CHASE M W J Exptl Med 69 767 1939

¹⁸⁰ RIEHM W Zentralbl f d ges Tuberk Forsch 36 337 1933

¹⁸¹ SIMON F A and RACKEMANN F M J Allergy 5 451 1934

¹⁸² PETRAGIANI G Pol clinico sez med 29 446 1922

¹⁸³ SHERMAN H KAPLAN C and WALZER M J Allergy 9 1 1937

¹⁸⁴ WALZER M J Immunol 14 143 1927

¹⁸⁵ RATNER B and GRUHL H L J Clin Invest 13 51 1934

maintaining a state of constant immunization against protein ordinarily ingested.

The long-debated question as to whether allergenic absorption takes place from the stomach was answered by the experiments of Straus, Harten, Gray, and Livingston. After both ends of the stomach and esophagus had been cut and clamped, and a few cubic centimeters of cottonseed emulsion introduced, absorption of the allergen was demonstrable in from two to eleven minutes.

Not only proteins but also such nonprotein substances as drugs are capable of inducing allergization by means of enteral resorption. As an example, we might cite nirvanol: after ingesting this substance for a sufficient length of time, the majority of individuals will respond with allergic manifestations resembling those of serum sickness.

It is relatively easy to achieve experimental allergization of the gastro-intestinal tract by way of the mouth. It often ensues (1) when the antigen consists of an infrequently eaten proteinogenous food, or (2) when the antigen is administered in great quantity, or (3) when resorption is facilitated by organic or functional disorders of the mucous membrane that increase the permeability. It has often been observed that guinea pigs can readily be allergized by oral administration of substances that are unusual for them—e.g., horse serum (Rosenau and Anderson; Auchincloss; Hettwer and Kriz), raw horse meat (Rosenau and Anderson), milk (V. Vaughan), egg (Laroche, Richet, and Saint-Girons), ascaris and taenia extracts (Morenas). Ratner and Gruel¹⁴⁸ found that both mature and young animals could be allergized and shocked by means of oral administration of protein foods in large quantities.

Gutzeit¹⁴⁶ demonstrated the significance of inflammation of the intestinal mucosa by the following experiment. An individual with a normal gastro-intestinal tract had a skin site passively allergized with serum from a patient allergic to fish (Prausnitz-Kuestner technic). He was then given 50 cc. of a fish extract by means of a stomach tube. There was no subsequent skin reaction. However, under similar conditions, an individual suffering from

gastro-enteritis reacted with severe erythema and a wheal at the prepared site. Moreover, when the normal individual was given four times the above named quantity of allergen by way of the stomach, he also had a positive skin reaction. We are, therefore, entitled to assume that the gastro-intestinal walls—in normal as well as in diseased human beings—are permeable to unaltered protein, but that there is a considerable difference in the degree of protein resorption, inasmuch as relatively small quantities of protein are resorbed only by the diseased gastro-intestinal mucosa, while greater quantities of protein will allow resorption even by the normal mucous membrane.

In animal experiments, it is possible to achieve speedier allergization by irritating the gastro-intestinal tract—as, for example, by means of alcohol (Hajós). Furthermore, the degree of resorption can be greatly increased by removing the protective layers of mucus covering the mucous lining. Arlong and his associates¹⁴⁷ used ox gall for this purpose. They reported that they were thus able to allergize guinea pigs to antipyrine, quinine, and olive oil.

As Table 7 shows, the addition of the saponin glycyrrhiza will increase the allergizing properties of an antigen many fold, because of enhanced resorption resulting from its action in dissolving the mucus. By this means, Urbach and Kitamura¹⁴⁵ were able to allergize animals even to type-specific propeptans.

Oral allergization may also take place by way of *mother's milk*. Donnally¹⁴⁹ demonstrated conclusively that antigens ingested by the mother could pass into the milk in an unaltered state. Brunner and Baron¹⁵⁰ confirmed these findings, using cottonseed protein. They did this with milk specimens obtained two and a half to twenty-four hours after the mother had ingested cottonseed. Cases illustrating this mechanism have been described by O'Keefe and Scott, Shannon, Balyeat, Ratner, and others. If egg, cottonseed, and other food proteins appear in the mother's milk, we must assume that, with the

¹⁴⁷ ARLONG, F., LANGERON, L., and SPASITCH, B. *Compt. rend. Soc. de biol.* 91: 913, 1924.

¹⁴⁸ CRACHE, E., and KITAMURA, S. *Klin. Wochenschr.* 13: 1576, 1934.

¹⁴⁹ DONNALLY, H. H. *J. Immunol.* 19: 15, 1930.

¹⁵⁰ BRUNNER, M., and BARON, B. *J. Allergy* 13: 377, 1942.

¹⁴⁶ GUTZEIT, K. *Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselk.*, 11th meeting, 1932, p. 92.

start of breast feeding, infants are immediately exposed to all the antigens consumed by the mother. Hence, it is not unreasonable to believe that in certain infants allergization may start at birth or within a day or two thereafter. Kwit and Hatcher¹⁹¹ proved that various drugs behaved in a similar manner. Bromides are transmitted through human breast milk in quantities sufficient to be readily demonstrable chemically and to produce constitutional effects on nurslings, including a slight skin rash in one case (Tyson, Shrader, and Perlman¹⁹²). Nicotine is similarly found in the milk of cigaret smoking mothers, although the nurslings were apparently unaffected presumably due to an acquired tolerance to the drug (Perlman, Dannenberg, and Sokoloff¹⁹³).

considerable quantities of egg white or horse serum were injected into a pregnant rabbit. Traces of these allergens could be detected by precipitin reactions in the fetal blood. These findings have been confirmed by Holford¹⁹⁶, Rosenau and Anderson, Otto, Doerr and Seidenberg, and especially Ratner and his associates have demonstrated that if a pregnant guinea pig is given large doses of horse serum or egg white several weeks before labor, the offspring will be passively sensitized to the protein by the mother's antibodies. The placental transmission of antibodies was demonstrated by Sherman, Hampton, and Cooke¹⁹⁷. Ratner and his associates¹⁹⁸ also demonstrated that when the mother was allergized just prior to delivery, the offspring would become actively allergized. The aller-

TABLE 7—Effect of Addition of Saponin on Degree of Enteral Allergization of Guinea Pigs

Enteral Allergization	Interval	Concentration of Allergen (dilat on of egg white necessary for elicitation of anaphylactic shock in 1 cc. doses)	Clinical Manifestations
Egg white alone (0.1 Gm. by mouth daily for 7 days)	2 weeks after last previous ingestion	1:10,000	fatal anaphylactic shock
		1:100,000	slight pruritus
		1:1,000,000	no symptoms
Egg white + 0.1 Gm. of glycyrrhiza each day	2 weeks after last previous ingestion	1:100,000	fatal shock
		1:1,000,000	fatal shock

Passive transfer of circulating antibodies from mother to young by the mammary route was first demonstrated by Ehrlich in 1892. Temporary immunity to virus diseases in nursing rabbits and mice can be effected by this means (Rosahn and Hu,¹⁹⁴ Berry and Slavin¹⁹⁵).

As regards the question of *transplacental* allergization, the majority of investigators now agree that it is possible to achieve it experimentally, both actively and passively. Transmission of foreign protein as such through the placenta was first demonstrated by Ascoli (1902). He found that when

gic state can be transferred to the second generation (Lehner and Rajka,¹⁹⁹ Cohen and Woodruff²⁰⁰). By means of Schick tests and determination of antitoxin titers, Liebling and Schmitz²⁰¹ showed that active diphtheria immunization of pregnant women resulted in increased antitoxin titers of their offspring for the first year of life.

According to Ratner,¹⁹⁷ the placenta in human beings and in rodents has only one connective tissue layer separating the maternal and the fetal blood, and this layer is permeable to antibodies and proteins. Nathan

¹⁹¹ KWIT N. T. and HATCHER R. A. *Am. J. Dis. Child.* 49: 900 1935.

¹⁹² TYSON R. M., SHRADER E. A. and PERLMAN H. H. *J. Pediat.* 13: 91 1938.

¹⁹³ PERLMAN H. H., DANNENBERG A. M. and SOKOLOFF N. *J. A. M. A.* 120: 1003 1942.

¹⁹⁴ ROSAHN P. D. and HU C. K. *J. Exper. Med.* 62: 331 1935.

¹⁹⁵ BERRY G. P. and SLAVIN H. B. *ibid.* 78: 305 1943.

¹⁹⁶ HOLFORD F. E. *J. Bact.* 11: 105 1927.

¹⁹⁷ SHERMAN W. B., HAMPTON S. F. and COOKE R. A. *J. Exper. Med.* 72: 611 1940.

¹⁹⁸ RATNER B., JACKSON H. C. and GRUHL H. L. *J. Immunol.* 14: 291 1927.

¹⁹⁹ LEHNER E. and RAJKA E. *Dermat. Wchnschr.* 81: 1731 1925.

²⁰⁰ COHEN M. B. and WOODRUFF B. H. *J. Allergy* 5: 437 1937.

²⁰¹ LIEBLING J. and SCHMITZ H. E. *J. Pediat.* 23: 430 1943.

Larrier's²⁰² report is especially interesting. He found that by means of certain substances—such as relatively small oral doses of sodium oleate, sodium ricinoleate, or bile salts—it was possible, without causing any damage, to make the placenta permeable to antigens. This finding is of particular practical significance, for pregnant women may, by taking certain laxatives or drugs, bring about allergization of the fetus.

Ratner is of the opinion, shared by the authors, that active intra-uterine allergization in human beings is a common occurrence, while passive sensitization takes place less frequently. In the former instance, the antigen, consumed by the mother in excessive quantities, is assumed to penetrate the placenta and to allergize the offspring. This, according to Ratner, occurred in those patients with infantile dermatitis, asthma, or vomiting in whom the first ingestion of certain foods produces the symptoms and who show positive skin reactions to the food. In the instances of passive placental allergization, the child becomes sensitized by the passage of the mother's antibodies through this organ. Walzer²⁰³ does not support these views. He points out that no one has proved in man that antigenic stimulation has taken place *in utero* and not by way of the mother's milk. Tuft¹¹² doubts the occurrence of passive allergization of the human fetus by maternal antibodies, and considers active intra-uterine allergization a more likely possibility.

The writers are of the opinion that—in a given case—it is often very difficult to decide whether the infant's allergization has taken place by way of the placenta or of the mother's milk. As an example, we might cite a case reported by Lyon. After nursing twenty-one days, an infant developed urticarial swellings over the entire body. Tests showed that the infant was hypersensitive only to its mother's milk. The mother was a poor mountain peasant whose diet for years had consisted chiefly of dried white beans. The infant's skin manifestations disappeared just as soon as the mother eliminated the white beans from her diet and reappeared when the

mother again ate this food. Granted that present immunologic methods do not justify a definite decision, we are rather inclined to assume a transplacental allergization in those cases in which the mother, during pregnancy, over-indulged in such foods as chocolate, eggs, milk, or white beans, and in which elimination of these foods from the mother's diet is followed by the disappearance of the infant's allergic symptoms.



FIG 10 PLACENTAL ALLERGIZATION
Bromide hypersensitiveness (bromoderma tuberosum)
in 9-week-old infant
(Courtesy Dr A. Krynski)

A definite case of intra-uterine allergization was reported by Krynski.²⁰⁴ A 9-week-old infant was given calcium bromide. Several days later, the child's face and head presented pea-sized nodules of bright-red color, with an uneven surface—in short, a typical bromoderma (Fig. 10). The mother, it was then learned, had taken considerable quantities of a medicine containing bromide—but only during the fourth month of pregnancy.

Absorption of allergens from the *uterine cervix* was shown to be a normal phenomenon

²⁰² NATHAN LARRIER, L. Bull. Acad. de méd., Paris, ser. 3, 109-57, 1933

²⁰³ W. W. WALKER, M. J. Allergy 9, 64, 1937

²⁰⁴ A. KRYNSKI, A. Poln. Dermat. Soc., April 26, 1937

by Rosenzweig and Walzer,⁹⁶ reactions appearing in passively sensitized skin sites within from nine to twenty five minutes. Absorption from the vagina occurred in about one-third of the tests, requiring from forty minutes to two hours.

Finally, the possibility of active allergization by way of the *rectum* should not be overlooked in view of the widespread use of rectal suppositories (Hajós). It should also be noted that M. Walzer and his associates have demonstrated passive allergization by depositing the antibodies in the rectal mucosa.

In conclusion, we may mention briefly the attempts to inhibit the process of allergization. In this connection, Haxthausen¹⁷⁶ reported that freezing with solid carbon dioxide at the site of application of the allergizing agent inhibited allergization in about 80 per cent of the instances in which it was tried. Of greater practical significance is Sulzberger's¹⁰⁶ report that skin allergization from an intracutaneous injection of neoarsphenamine can be prevented if an intravenous injection is given twenty four hours later. Hyposensitization, however, could not be achieved by such an injection when given after the hypersensitiveness had already developed. For a discussion of various attempts at influencing sensitization by the administration of vitamins, the reader is referred to page 68. Other factors affecting allergization are considered in the next chapter and in the section on experimental anaphylaxis in chapter VI.

D ALLERGIC EQUILIBRIUM

It is not infrequently observed—especially in food and drug allergies—that the causative ingested will on one occasion elicit allergic manifestations but at another time fail to do so. To indicate this situation, Vaughan has suggested the term "allergic equilibrium." He assumes that these patients are temporarily in better balance as regards their reactive capacity.

There can be no doubt that "allergic tolerance" varies from time to time depending on conditions within the individual, and depending also on contributory and precipitating factors that may raise or lower the threshold of

tolerance. These factors involve—as shown by the examples in the succeeding chapter—the endocrine glands, the autonomic nervous system, gastro intestinal resorption, infections, and meteorologic or psychosomatic influences.

Furthermore, there are other possible explanations of this apparent variability in the patient's capacity to react—for example, the fact that two or more allergens acting together will disturb the patient, whereas either one alone, even in large doses, may have no effect. This would seem to indicate that the interrelationship between these two agents forms a combination to which the patient is allergic. The following case will illustrate this. A trained nurse reacted to ingestion of omelettes with urticaria, but was able to tolerate raw or cooked eggs, milk, and flour when each of these ingredients was taken separately. Adelsberger and Munter reported two cases of migraine, in one of which attacks occurred only after eggs and tomatoes were eaten together, in the other, reactions were regularly seen to follow the ingestion of mayonnaise, but not of eggs or oil separately. An interesting combination involving one food and one drug (fish and codeine) was observed by Fechner. Other concatenations of circumstances may be necessary. In a young woman observed by the junior author, 0.3 or 0.6 Gm. (5 or 10 grains) of acetylsalicylic acid taken after a drink or two of alcohol would produce urticaria and angioneurotic edema—but only provided the patient was in the midst of a menstrual period. The absence of any one or two of these factors was sufficient to prevent the reaction.

Although the allergic state represents a qualitatively altered reaction capacity, in many cases a roughly quantitative relationship can be discerned. In brief, the actual allergenic exposure must exceed the patient's threshold at the moment. Critical evaluation of this point in many cases of hay fever, asthma, poison ivy dermatitis, and other diseases will often explain away apparent fluctuations in the allergic equilibrium. In food allergy, particularly, quasi cumulative effects are not infrequently seen. Thus, the ingestion of the allergenic food once or twice may be harmless, but repeated daily consumption for a few days may result in an explosive reaction with clinical manifestations. The

⁹⁶ ROSENZWEIG M. and WALZER M. *J. Allergy* 9: 395 1938

¹⁰⁶ SULZBERGER M. B. *Arch. Dermat. & Syph.* 20: 669 1929

patient may then enter a refractory state for a while, even if the responsible foods are still taken.

Rinkel¹⁰⁷ has gone so far as to divide food allergy into a fixed type, which shows no variation in the sensitization, and a cyclic type with intermittent sensitization, tending to vary depending on exposure to the allergenic food. In the latter, during a period of elimination of the food, there will be successive stages of hyperacute sensitization, active average degree of sensitization, latency, and tolerance. If the food is now re-admitted to the diet, the period of tolerance persists for a while, followed by latency, active average sensitization, and finally masked sensitization. The cycle may be repeated indefinitely.

Other instances have been explained by the fact that specific hypersensitiveness is a reaction to secondary—and not to primary—antigens. In other words, the patient is not hypersensitive to a food or drug per se, but to products of intermediate digestion or altered

metabolism that are formed, for example, as the result of a coincidental constipation or colitis.

Still other cases seem to depend on the fact that the given ingestant is in itself merely a partial antigen (hapten) that becomes a complete antigen only after conjugation with body protein altered as a result of infections, burns, gastro-intestinal disorders, etc (p. 116). Therefore, in the absence of such conditions, the food or drug cannot produce allergic symptoms. Koenigsfeld's¹⁰⁸ observation on himself may serve as an illustration: he suffered from asthmatic attacks due to amidopyrine only when he coincidentally had grippe with high fever.

Regardless of which of the above possibilities applies in a given case, or even if no plausible explanation can be found, the fact remains that considerable variations in the degree of allergic reactivity are frequently seen in human allergies.

¹⁰⁷ RINKEL, H. J. *Ann Allergy* 2, 115, 1944.

¹⁰⁸ KOENIGSFELD, H. *Ztschr. f. Klin. Med.* 102 129, 1926.

PREDISPOSING AND CONTRIBUTORY FACTORS IN ALLERGY

THE INITIATION of allergic disease depends on two fundamental factors (1) the *auxiliary conditions* that predispose the organism to allergization and that may therefore be considered as paving the way for the allergy (2) the *exciting allergens* which actually elicit the allergic reaction. As we have stated elsewhere, the element of exposure alone—i.e., exposure to massive quantities of allergen—can under appropriate conditions suffice to bring on an allergic state without the mediation of any predisposing factors. However, this is a relatively rare occurrence in man.

Sometimes the auxiliary conditions are not so much predisposing as contributory. For example, an upper respiratory infection may initiate an allergic asthma due to dust, here the infection is clearly predisposing. Contrariwise, when a primary dust asthma already exists and is aggravated during a respiratory infection, the latter is a contributory factor.

The present trend to search only for the exciting allergen without regard to the basic importance of the ancillary influences may be the reason why allergic therapy is often so unsatisfactory. For example, the elimination of certain foods will produce a temporary freedom from symptoms, the physician will then be surprised and disappointed when he observes that administration of a drug causes a recurrence of the same or a different clinical type of allergy. If, in addition to removal of the exciting allergen the underlying predisposing factor, such as a chronic gastroenteritis, an endocrine dysfunction, or even a psychic strain, is corrected, we can often achieve lasting freedom from the allergic disease. It is therefore of the greatest importance that equal attention be accorded in search and treatment to both eliciting causes and auxiliary conditions. Of course identification of the predisposing factor or factors in a given case of allergy may be even more difficult than discovery of the eliciting allergen. In the first place, no possible testing can bring direct proof of the fact that, for instance, an infection or a gastro intestinal disturbance has

acted as a predisposing circumstance the results of properly applied therapy may be the only definite indication of the nature of the predisposing condition. In the second place it must be remembered that not infrequently two or more influences sometimes completely unrelated—but often bearing a definite interrelationship—must combine to pave the way for allergization. Thus we have observed a case of food allergy in which the patient manifested her state of hypersensitivity to a food only when she suffered from a respiratory infection during her menstrual period. In the third place, we must certainly admit that we are not aware of all the factors that might possibly come into consideration.

Because of the basic importance we attribute to the predisposing factors, we shall discuss them in some detail.

A HEREDITY

For years, the theory was almost universally accepted that heredity plays the leading part in the establishment of an allergic state. Today, however this viewpoint has again become the subject of considerable controversy. It has always been recognized of course, that what is inherited is not the allergic disease itself—that is the clinical type of reaction—but merely the allergic tendency (in other words the capacity for a pathologically increased physiologic reactivity). This would explain how, for example, while a father may have hay fever his son may develop a "horse asthma," and his daughter may present an urticarial response to milk. The theory of heredity found support in statistics showing that more than 50 per cent of allergic patients gave positive allergic family histories (Spain and Cooke, Cooke and Vander Veer, Bray, Duke, Lima, van Leeuwen) while the general population reported family histories of allergy in only 7 to 12 per cent of cases. However, Coca points out—and in our opinion rightly so—the possible errors that may seriously affect the value of statistical studies

of the hereditary nature of allergy. We shall take up these considerations below.

We have, we believe, conclusively shown elsewhere (p. 45) that the capacity for becoming allergized is a characteristic possessed by all members of the human race and that under certain experimental conditions of exposure it is possible to achieve allergization to a great variety of substances in 100 per cent of the subjects. If this is so, then heredity cannot have the overwhelming importance that is conspicuously implied in the subdivision of hypersensitiveness, on this ground, into atopic and nonatopic types.

Does heredity play any part in the pathogenesis of allergy? We cannot go quite as far as Ratner,²⁰³ who, on the basis of his own investigations (see below) categorically denies that heredity plays any rôle whatever. We are of the opinion that heredity is to be considered as one of the major factors predisposing to allergy; but we dispute the assumption that heredity constitutes a necessary prerequisite.

Our viewpoint is based on the following facts. In the first place, according to Doerr²¹⁰ and other experienced investigators, everything that has been said to date concerning the hereditary factor in allergy is pure assumption: for it has never been possible as yet to prove the hereditary nature of allergic diseases. Nor, furthermore, have any animal experiments been reported to demonstrate that a given form of allergy is inherited according to the mendelian laws (Dahlberg⁷⁰). The apparent inheritance of anaphylaxis demonstrable in animal experiments must be regarded, according to the investigations of Ratner, of Cohen and Woodruff, and of others, as a result of active or passive intra-uterine allergization. The argument against the factor of heredity and for intra-uterine allergization is also supported by the fact that the mating of anaphylactic male guinea pigs with normal females produces normal offspring, while the mating of anaphylactic female guinea pigs with normal males produces allergized offspring. On the other hand, it is possible by selective breeding experiments to develop strains of guinea pigs that can be more easily and strongly allergized to chemicals, poison

ivy, and other substances. This sensitization is specific. These experiments of Chase⁸⁴ and Jacobs and his associates²¹¹ demonstrate the existence of variations of a hereditary nature in the capacity for allergization, at least as regards the skin. However, this apparent inheritance of the capacity for the development of tissue antibodies may possibly be otherwise explained (Rackemann²¹²). It may involve inbred differences in the permeability of the skin and/or the gastrointestinal tract making the tissues more accessible to the foreign substance, or in the capacity to release H-substance, or even in the ability to react to the H-substance.

After critical consideration of the available evidence, Zinsser, Enders, and Fothergill¹¹ arrived at the conclusion that "heredity indicates merely a disposition to sensitization. In the relatively few cases in which reactions occur upon first contact, there is probably a marked previous exposure, possibly intra-uterine." According to Kolmer,¹² what is inherited in allergy is the instability of the vasomotor system that renders the organism more susceptible. On the other hand, Cooke and Vander Veer, Balyeat, Hanhart, and others, on the basis of family histories of their allergic patients, claim that hypersensitiveness is inherited as a dominant characteristic in accordance with the mendelian laws. Children with bilateral inheritance acquire allergic diseases in 75 per cent of cases, and those with unilateral inheritance, in 50 per cent, as compared with an incidence of 7 to 12 per cent among those without family histories of allergy. The heavier the inheritance, the earlier the age at which the symptoms appear.

But these assertions have also been contradicted. Wiener and his associates²¹³ dispute the assumption that allergy is inherited as a simple mendelian dominant. They point out that in their material both parents were found to be normal in more than half of the cases examined. They therefore postulated a theory of incomplete dominance, holding that individuals heterozygous with respect to the allergic gene may develop

²⁰³ RATNER, B. J. *Allergy* 8: 213, 1937.

²¹⁰ DOERR, R. *Handb. d. inn. Med.* # (pt. 1), 445, 1926.

²¹¹ JACOBS, J. L., KELLEY, J. J., and SOMMER, S. C. *Proc. Soc. Exper. Biol. & Med.* 45: 639, 1941.

²¹² RACKEMANN, F. M. *Arch. Int. Med.* 71: 107, 1943.

²¹³ WIENER, A. S., ZIEVE, I., and FRIES, J. H. *Ann. Eugenics* 7: 141, 1936.

allergic diseases at a later average age in life or not at all, but are nevertheless capable of transmitting the tendency to offspring while when no allergic genes are inherited, allergy will not develop

Ratner²¹³ in an exhaustive investigation of 250 allergic and 350 normal children reports that the incidence of allergy in the families of the allergic children is approximately the same as in that of the normal children—from 7 to 10 per cent. Moreover, further analysis of this group revealed that heredity had little influence as regards the age of onset of the allergic symptoms. Ratner and his colleagues²¹⁴ hold that the difference in the ages at which allergic syndromes appear is dependent on the allergen and the type of allergic disease rather than on genetic differences.

Wiener²¹⁵ expresses a broad and wholly tenable viewpoint: "The discussion of the relative importance of heredity and environment, or nature and nurture is also a bit irritating to a geneticist, since he knows that both are important, the relative importance depending on the circumstance. Thus, under normal conditions, everybody has equal exposure to pollen, when they live in the same locality, then the development of hay fever or pollen asthma will depend mainly on one's response to the exposure, or the constitution. Where constitutional differences exist, these are susceptible to genetic analysis. On the other hand, where the exposure is marked and the allergen is potent, as with contact dermatitis due to primrose, poison ivy, etc., the constitutional differences are relatively insignificant."

Comparing hay fever in different countries is a more complicated affair since here we have to deal both with constitutional and environmental differences in varying proportions, so that in one case heredity may appear more important, and in other cases environment more important. The only way to study heredity in allergic disease or in any condition susceptible to modification by environment, is to maintain a constant environment. This is of course not entirely feasible in such complicated conditions as the allergic diseases, so that the

formulation of any theory can at best only be approximate. Human beings differ with regard to their degree of allergy, while guinea pigs show little difference in this regard. That is why anaphylaxis is an irregular and uncommon phenomenon in man (luckily), while it can regularly be elicited in guinea pigs. Even the latter exhibit differences, however, when it comes to contact dermatitis induced by experimental applications of small amounts of the excitant."

Weiss and English²¹⁶ suggested that apparent hereditary relationships may rather be explained by psychosomatic factors. Thus, a child can absorb the behavior pattern of some member of the household to whom he is intimately attached, and then in later life subconsciously imitate the illness of that person. Hence, what we often think of as a hereditary influence may in truth be an environmental problem dating back to the earliest days of infancy.

We shall not deny the fact that particularly in families with strong tendencies to asthma, for example, the offspring are more likely to develop asthma than hay fever. This organ determination of the allergic predisposition is well illustrated by a family reported by Hanhart, in which projectile vomiting due to food occurred in 6 of 21 members in three generations. Stiles and Johnston²¹⁷ studied a family in which 22.4 per cent of 232 persons in five generations suffered from respiratory allergies. This tendency is also known with reference to angioneurotic edema of the glottis, as discussed in more detail on page 759. Such organ predisposition, however, is considered as due more to the factors of exposure, and to some extent to psychic influences, than to heredity.

Furthermore, it is a common observation that a highly specific hypersensitivity to a single food, drug, or inhalant will "run" in families. One observation of the authors' may suffice to illustrate this. The patient suffered from an urticaria due to wild strawberries. Two of his children reacted to the same food with rather severe symptoms of gastro-intestinal allergy (vomiting, diarrhea,

²¹³ RATNER B, SILVERMAN D E and GREENBURGH J E J Allergy 12 272 1941

²¹⁴ WIENER A S personal communication

²¹⁶ WEISS E and ENGLISH O S Psychosomatic Medicine Philadelphia Saunders 1943

²¹⁷ STILES K A and JOHNSTON E J J Allergy 17 11 1946

vertigo, and collapse). One grandchild incurred urticaria from strawberries. It is interesting to note that all these allergic manifestations were elicited only by wild and not by cultivated strawberries.

Finally, attempts have been made to solve the question of heredity by investigation of identical, uniovular twins. No uniformity of results has been obtained in this, either. It must be admitted, however, that the majority of authors (Spaich and Ostertag, Benson, Credille, Fineman, Bueno, Urbach, and others) found allergic phenomena of similar or different types in the twins. A study by Hanhart of 71 pairs of identical twins revealed 80 per cent correlation in respect to hay fever, 60 per cent in migraine, and 28.6 per cent in asthma. On the other hand, M. B. Cohen and also I. S. Kahn, as well as Urbach, have reported on several pairs of twins—observed for years—in which one twin developed active allergy and the other did not.

B. CONSTITUTIONAL INFLUENCES

Brandt employs the term "allergic constitution" to designate not so much the commonly shared capacity of all members of the human race to react with allergic phenomena, as the peculiarity in a single individual of becoming hypersensitive to such substances in such amounts and by such administration of them as will not induce an allergic response in the overwhelming majority of human beings.

Constitution in this sense signifies bodily condition as manifested in the manner of reaction to external stimuli. The *anatomomorphologic* school sees in the bodily structure the expression of the constitution. Investigations along these lines have revealed the fact that allergic individuals do not belong to any special body type or types. On the other hand, the *clinical-functional* school, headed by W. Jaensch, recognizes two constitutional types that must be considered in their relation to allergy, namely, the hyperthyroid and the tetanoid type. In the former, the autonomic nervous system evidences a high degree of excitability, most clearly expressed in the irritability of the sympathetics. Concurrently, there is a state of excessive sensitivity of the entire organism to external irritants and to psychic influences.

Furthermore, there is a tendency to exudative processes of the skin and of the mucosa. The allergic diseases are certainly related to this condition of the body—a condition that can probably be explained on the basis of an increase in thyroid activity (von Bergmann). The tetanoid type, on the other hand, is distinguished by excitability of the entire nervous system, clinically expressed by a general tendency to smooth-muscle spasm. This condition is probably attributable to a decrease of parathyroid function in the hormonal interplay. This group is understood to include those cases of asthma that are distinguished by vagotonia and in which one can assume a tendency to spasm on the part of the bronchial musculature.

The *constitution of the skin* appears to be of special significance in the acquisition of allergies. Stokes and Garner²⁶ emphasize the fact that a seborrheic state makes the skin susceptible to pyogenic and yeast infections that may act as predisposing factors. An excessively dry and easily fissured skin (ichthyotic state), as well as a soft moist easily macerated skin (owing to hyperhidrosis), predisposes to epidermal allergization, i.e., contact dermatitis. We should also include Burckhardt's²⁷ observation that certain skins are not capable of neutralizing solutions of alkali placed on their surface as efficiently as normal skins do. Individuals whose skins show this inefficiency with respect to alkali neutralization are more readily allergized to certain substances.

The influence of local vascular disturbances may also be noted here. Thus, venous stasis in the lower leg is the predisposing factor in dermatitic affections of that region (frequently due to auto-allergization to skin protein altered as a result of scratching, see p. 126), and hemorrhoids are predisposing to medicamentous anal dermatitides.

According to Rost, individuals with neurodermatitis are distinguished by a definite constitutional type: the hair is scant, the skin dry and pale gray (Rost attributes this color to the constant state of contraction of the vessels of the plexus subpapillaris); the blood pressure is usually low; the blood sugar level is low, and

²⁶ STOKES, J. H., and GARNER, V. C. *Am J M S.* 191, 566, 1936

²⁷ BURCKHARDT, W. *Arch f Dermat u Syph* 173: 155, 1935

even in the course of a glucose tolerance test the curve does not rise sufficiently, and gastric hypo- or anacidity is often observed (Urbach). According to van Leeuwen, there is a decrease in the binding capacity of the blood for salicylic acid. A review of these stigmata makes it apparent that in neurodermatitis the constitution is the principal factor in the abnormal reactivity of the skin, and that the allergen merely assumes more or less, the function of acting as the eliciting factor.

These few remarks will suffice to indicate that what is commonly known as the body constitution is capable of exerting an appreciable influence on the type and course of an allergic disease, and is thus to be considered as

thetic nervous system results in the production of an epinephrine like substance.

In Table 8 an attempt is made to summarize the present state of our knowledge of the influence of the endocrine glands on experimental anaphylaxis. For further information, the reader may consult critical reviews by Farmer²¹⁸ and Harkavy.²¹⁹

Haag and his associates²²⁰ point out that the effect of hormones on acute anaphylactic shock must be distinguished from their effect on allergic reactivity. To demonstrate this, they administered a given endocrine extract in the last twenty-four to forty-eight hours before the lethal dose in order to influence the shock, in the preceding two weeks, it was

TABLE 8—*Effect of Endocrine Products (Hormones) and Extirpation of Endocrine Glands on Experimental Anaphylaxis*

Enhancing Effect	Inhibiting Effect	No Effect
Thyroxin Insulin Adrenalectomy Ovariectomy Hypophysectomy	Epinephrine (adrenalin) Parathyroid Pituitrin Thyroidectomy Parathyroidectomy Thymectomy	Male and female sex hormones Hormone of anterior lobe of pituitary gland Adrenal cortical hormone

an important predisposing factor. Hill expresses it very clearly. "Practically everyone who has lived for any length of time is allergic, very few are so constituted that they have an allergic disease." However, the fact that under certain conditions every human being and every animal can be allergized, is evidence that a special constitution is not an absolute essential for the development of allergy.

C THE ENDOCRINE GLANDS AND THE AUTONOMIC NERVOUS SYSTEM

The importance of the endocrine glands and the autonomic nervous system as regards the allergic mechanism warrants their discussion together, in view of their intimate functional relationship. Recent investigations have revealed that, as a result of nervous impulses, certain substances are formed, the actions of which are similar to those of the products of certain endocrine glands, at least functionally. Thus, for example, irritation of the sympa-

thetic nervous system results in the production of an epinephrine like substance. The noteworthy fact was revealed that treatment with epinephrine (adrenalin) or pituitrin over a long period of time results in an appreciable increase in the animal's tendency to shock reaction. While epinephrine is capable of inhibiting an acute anaphylactic attack and is therefore useful for symptomatic therapy, it is, on the other hand, preferable to employ for specific treatment preparations that do not contain this drug. Skin and liver extracts produce marked lowering of the tendency to shock, and parathyroid extracts a slight lowering. This finding conforms with clinical observations with regard to skin and liver preparations.

Animal experiments and clinical observation by Wittich²²¹ indicate that there is no rational

²¹⁸ FARMER L. *Ann Int Med* 17: 212 1942.

²¹⁹ HARKAVY J. *J Mt Sinai Hosp* 10: 565 1944.

²²⁰ HAAG F, E KONIG H, HUMMELSTEIG K, ROBER G and CRAMER A. *Ztschr f Immunitätsforsch u exper Therap* 91: 419 1933.

²²¹ WITTICH F W. *Ann Allergy* 1: 124 1943.

basis for employing adrenal cortical extracts in allergic states. However, posterior pituitary lobe extract, by reason of its constrictive effect on arterioles and capillaries, appears to have an antagonistic action on cholinergic drugs such as histamine, and when administered along with epinephrine, prolongs or enhances its effect.

It is interesting to note that combinations of hormones act differently than do the hormones separately. For example, epinephrine plus parathyroid extract decreases the tendency to shock reaction.

Table 9 presents a summary of the influence of the endocrine glands and of their products on human allergies.

On the basis of animal experiments, we may now definitely assume that the *thyroid gland* plays a part in the production and course of allergic reactions. Thus, it has been

urticaria, appear to be more commonly associated with hypothyroidism. Appropriate therapy of the endocrine disorder has a beneficial effect on the allergic disturbance. Koch²⁴ holds that the great majority of patients with recent evidences of allergy tend to exhibit downward deviations from the normal in the functions of the thyroid and adrenals, and especially those of the entire pituitary gland. In support of this concept, he cites the changes in the water and salt metabolism of the shock tissues, as well as changes in blood chemistry. Wilensky²⁵ has gone so far as to suggest that thyrotoxicosis is of allergic pathogenesis, with the thyroid apparently acting as an antigenic and/or catalytic agent in a sensitized person.

It is well known that *menstruation*, the *menopause*, and *ovarian dysfunctions* are factors tending to enhance existing states of allergy.

TABLE 9—Effects of Endocrine Glands and Their Products on Human Allergies

Enhancing Effect	Inhibiting Effect	No Effect
Hyperthyroidism	Mixedema	Hormone of anterior lobe of pituitary gland
Menstruation	Pregnancy	Thyroidectomy
Menopause	Epinephrine (adrenalin)	Parathyroidectomy
	Pituitrin	Thymectomy
	Parathyroid extract	

demonstrated that thyroidectomized animals cannot be allergized or rendered anaphylactic, the capacity for allergization is regained, however, after feeding or injection of thyroid (Eickhoff²⁶). Moreover, guinea pigs that have been allergized with plant protein, and then injected with a thyroid preparation, manifest considerably more severe anaphylactic responses than do the merely allergized control animals. On the other hand, it is possible to elicit anaphylactic manifestations in guinea pigs whose thyroid glands are removed after allergization (Blom).

Regarding clinical observations, Epstein²⁷ has found that the endocrine functions most commonly associated with allergic states are related to the thyroid gland. Thus he reported 4 cases of asthma in patients with hyperthyroidism, while certain allergies, such as angioneurotic edema, hay fever, and

Whether this is a specific hormonal or a non-specific neurovegetative influence must be determined in each individual case. As examples, we may cite the numerous cases of pre- and postmenstrual asthma and the frequent association of migraine with the menstrual cycle. L. Freund reported the case of a woman who consistently had an urticarial eruption on eating smoked sprats during the premenstrual phase of her cycle; at other times, however, she was able to consume the same amount of the same brand of sprats without difficulty. D'Amato described an interesting case of a 33-year-old woman who during her menstrual period regularly showed a definite cutaneous hypersensitiveness to light that disappeared after menstruation. After X-ray treatment of the ovaries, both the menses and the light hypersensitiveness did not recur for two years. In a number of

²⁶ EICKHOFF, W. *Virchows Arch f path Anat* 303: 481, 1929

²⁷ EPSTEIN, A. A. *J Mt Sinai Hosp* 12: 191, 1945

²⁴ KOCH, F. *Eye, Ear, Nose & Throat Monthly* 23: 493, 1944.

²⁵ WILENSKY, A. O. *Surg* 17: 61, 1945

our own allergic cases, failure of hyposensitization appeared to be due to the fact that, despite all the measures employed, it was impossible to overcome the amenorrhea. In other cases, complete cure was achieved by means of ovarian substitutional therapy or irradiation of the pituitary gland.

It is well to bear in mind, furthermore, that during menstruation the entire organism is in a state of heightened reactivity—smaller doses of antigen will suffice to elicit responses—and it is advisable, therefore, to suspend all allergic injections during this period.

Pregnancy, on the other hand—aside from the dermatoses of pregnancy, and eclampsia—has an influence tending, in general, to diminish an existing allergy. This can be observed quite frequently in cases of asthma, hay fever, and migraine. J. Jadassohn reported the case of a woman who always reacted to certain kinds of fruit with urticaria—except during her pregnancies. However, the allergic response of the skin to chemical excitants is generally stronger and more rapid in pregnant than in nonpregnant women.

The well known tendency of children to "outgrow" asthma and other allergic diseases may in large part be due to the profound endocrine alterations occurring during *puberty*. Thus, in a follow up study of a group of 351 asthmatic children, Brock²²⁶ noted spontaneous recovery at puberty in one-third and a marked improvement in a total of 80 per cent.

According to Yun, removal of the *testes* definitely reduces the readiness for anaphylaxis, regardless of whether castration is performed before or after allergization. The same author reports that, by injecting a testicular suspension in castrated animals and was thus able to restore their capacity for allergization.

Furthermore, recent investigations have shown not only that the endocrine glands can affect allergization, but also that the latter can influence the former. Thus, Eickhoff²²⁷ claimed that in experiments with rabbits and guinea pigs, specific sensitization resulted in changes in the thyroid gland (marked activity of the central axis of the gland) similar to the changes observed in the thyroid gland after artificial stimulation by the administra-

tion of thyroid extracts. Resection of the cervical sympathetic nerves prior to allergization prevented this response. After unilateral vagotomy—performed either prior or subsequent to allergization—a normal thyroid was found. Lee²²⁷ demonstrated that both unilateral and bilateral vagotomy augmented anaphylactic symptoms in experimental animals. Furthermore, administration of insulin inhibited the augmenting action of the vagotomy, and hypoglycemia induced by insulin was relatively less during anaphylactic shock.

The results of all these experiments demonstrate, once again, the close connection between the state of hypersensitiveness and the functions of the endocrine glands and of the autonomic nervous system.

Fowler²²⁸ reported an interesting instance of unilateral allergic rhinopathy in a patient with Horner's syndrome due to interference with the cervical sympathetic system following resection of the stellate ganglion. Eosinophils were present in the nasal secretions. Another case had homolateral nasal obstruction and watery rhinorrhea. However, the majority of cases of Horner's syndrome have no nasal symptoms.

It is well known fact that drugs that stimulate the parasympathetics favor allergization or tend to prolong an existing hypersensitiveness. This is the reason why many authors believe that a disturbance of autonomic equilibrium, together with an overexcitability of the parasympathetics, is the actual cause of the disposition to allergic diseases (Kolmer). It must be borne in mind, however, that the pharmacologic methods of testing with epinephrine, atropine, pilocarpine, and similar drugs determine merely the excitability of the peripheral nerve endings, and do not permit any conclusion as to the condition of the vegetative centers themselves. Furthermore, these vegetative poisons are not strictly selective in their action, they have a considerable tendency to amphotropic action, depending upon external conditions (e.g., the dose of the poison) and upon internal factors (behavior of the endocrine glands, etc.).

Just as the endocrine glands can be affected

²²⁷ LEE Y. C. J. Chosen M. A. (abstr. sec.) 24: 97, 1934

²²⁸ FOWLER E. P. Jr. Arch. Otolaryng. 37: 710, 1943

by the mechanism involved in allergization (see above), so may also the autonomic nervous system. In comparing the results of the pharmacologic responses of the autonomic nervous system before and after experimental allergization (e.g., with ursol, a commercial dye), Marquardt²²⁹ found that in subjects with vagotonia, sensitization increased the irritability of the parasympathetics, while in persons with sympathicotonia, the tone of the sympathetic portion was heightened.

From the clinical point of view, everyone dealing with allergic patients is impressed with the incidence of vasomotor instability or irritability. It is noteworthy that introverted personalities are much more frequently and more severely afflicted than are those that can react outwardly, so to speak. The "high-strung" individuals of both sexes are more likely to be affected than are more stolid and slow-reacting persons. The marked dependence of the capacity for allergization on autonomic imbalance or neurocirculatory instability is probably the reason why primitive people only rarely present allergies, and why the latter are observed only in domesticated and not in wild animals.

The rôle of the autonomic nervous system in allergy has recently been reviewed by Kuntz.²³⁰ He holds that the so-called allergic state probably does not exist in the presence of a normal functional status of the autonomic nerves. Some of the most characteristic manifestations of allergic disease (including increased smooth muscle tonus, vasodilatation of the mucous membranes, and increased secretory activity of the mucous membranes) appear to be causally related to a heightened parasympathetic or cholinergic reactivity. Either phasic or chronic cholinergic predominance as a type of autonomic imbalance is the rule in allergic disease, and accounts for the therapeutic efficacy of adrenergic or sympathomimetic drugs. The mode of action of such drugs in common use is indicated in Table 10 (Wittich¹³⁴).

It has been repeatedly pointed out that the limitation of the allergic reaction in human beings to a single shock tissue may be partly explained as a function of the parasympathetic

portion of the autonomic nervous system, since its discharge of impulses is ordinarily confined to a single organ or body region. The sympathetic nervous system, by contrast, tends to discharge *en masse* in diffuse form, influencing the whole body.

It is also noteworthy that parasympathetic or cholinergic hyperactivity is accompanied by a shift in the acid-base balance toward acidity, and conversely, changes in acid-base balance are accompanied by corresponding changes in the autonomic functional balance. This may account for some of the changes in blood chemistry noted in chapter VIII. Many of the therapeutic measures employed in allergic diseases, including those affecting the acid-base balance, certain types of dietotherapy, and psychotherapy, aim at a restoration of autonomic functional balance.

Finally, the opinion is now prevalent that diurnal variations in reactivity also depend upon the function of the endocrine glands or autonomic nervous system. This influence is exemplified by the fact that patients with asthma, urticaria, and other hypersensitivities often show a daily periodic pattern—for example, a considerable exacerbation after midnight or on first arising in the morning—that cannot be explained on the basis of the action of the allergen. Since the fluctuations to which most physiologic processes are subject depend upon endocrine activity, this explanation may also underlie the diurnal variations in the intensity of allergic responses.

Despite the importance of the neuro-hormonal regulatory mechanism, it must be reiterated for clarity of thought that hypersensitiveness is nevertheless basically a cellular reaction. This is illustrated by every experiment involving excised sensitized organs, such as the uterus or lung, as well as by autotransplantation in human beings (p. 154). Moreover, Schwartzman²³¹ was able to demonstrate tuberculin hypersensitiveness in explanted mononuclear leucocytes derived from tuberculous animals and grown by a tissue culture technic. In addition, Netter and Witebsky²³² elicited anaphylactic responses in the vascular system of the three day old chick

²²⁹ MARQUARDT, F.: *Dermat. Wechn.schr.* 100: 409, 1935.

²³⁰ KUNTZ, A.: *Ann. Allergy* 3: 91, 1945.

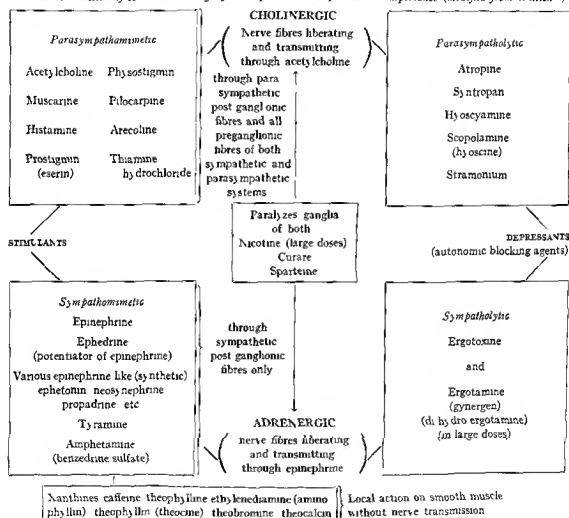
²³¹ SCHWARTZMAN, G.: *Arch. Path.* 6: 792, 1928.

²³² NETTER, E., and WITEBSKY, E.: *Proc. Soc. Exper. Biol. & Med.* 32: 724, 1935.

by means of anti rabbit serum and Forssman antisera, before any endocrines or nerves are developed and at a time when autonomic drugs are still ineffective. It would seem therefore that the neuro hormonal system may regulate but not initiate hypersensitiveness probably by influencing the threshold of response (Harkavy²¹²).

tein is a physiologic process. This is definitely shown by (1) demonstration of precipitins in the blood and urine of animals that have received foreign protein by mouth (2) determination of precipitins in the blood of nursing infants—normal ones as well as those with pathologic conditions of the intestines—occurring after the first ingestion of cow's milk.

TABLE 10—Action of Autonomic Drugs of Therapeutic and Experimental Importance (modified from H. H. H. H.)



D GASTRO INTESTINAL RESORPTION

To avoid repetition the reader is referred to the discussions on enteral allergization and allergic diseases of the gastro-intestinal tract (pp 46 and 679).

We are now aware of the fact that gastro intestinal absorption of unaltered food pro-

egg white, or even vegetable protein, these precipitins are to be found from eight to twenty five days after ingestion of the protein (O. Schloss and co workers), (3) demonstration of antibodies in the blood of 60 per cent of normal artificially fed infants by the complement fixation method (Gjorgy Moro, and Witebsky), (4) elicitation of the Prausnitz

Kuestner reaction by the peroral route (M. Walzer).

Detailed information regarding the speed of resorption of unaltered protein is afforded by the studies of A. and M. Walzer.²² They employed the so-called reversed technic (p. 147) and found that the time of resorption is generally between a half hour and two hours. As Ratner and Gruchl have pointed out, this physiologic resorption of food protein may serve the purpose of maintaining in the organism a continuing deallergization to the protein.

Under pathologic conditions, however, the degree of resorption can increase to such a point that allergization ensues. Examples of such pathologic conditions are to be found, especially in children, following excessive indulgence in foods such as eggs, chocolate, or bananas. The writers have also seen comparable cases of allergization in adults following excessive consumption of one particular food, chiefly in the form of a lichen urticatus or prurigo mitis. This occurred in farm girls who, on employment in delicatessen shops in the city, ate considerable quantities of highly spiced sausage. A diet free from animal protein promptly relieved the symptoms. When these patients were subsequently given a moderate quantity of the same sausage, there were no symptoms, indicating clearly that the excessive consumption had brought on excessive resorption. Similarly, it is possible to anaphylactize animals by repeated feeding on several successive days of an unaccustomed protein (e.g., egg, milk, horse serum).

A significant rôle is also played by insufficiency of digestive juices and especially by gastric hypo- or anacidity. This results in the ingested food entering the intestine too rapidly and in an inadequately digested state. Consequently there is resorption of products of incomplete digestion. For example, Bray,²³ in a group of 200 asthmatic children, found the gastric acidity to be markedly lower than normal and the incidence of achlorhydria increased. Moreover, in the presence of gastric hypoacidity there is insufficient bactericidal action, so that a pathologic intestinal flora may arise, which in turn provides an important factor predisposing to allergy. In

achylia, the digestion of carbohydrates is also impaired in that much undigested carbohydrate enters the intestines. A pancreatic insufficiency is very frequently associated with this condition. This may lead to diarrhea of gastrogenous or pancreatogenous origin, or to enterocolitides due to putrefaction or fermentation, with subsequent pathologic resorption.

The fact that hypo- or anacidity constitutes an important factor—particularly in alimentary allergies—is well known to clinicians, and is taken into due consideration in the therapy (Barber and Oriel, J. H. Stokes, A. and M. Walzer, Gray and M. Walzer, Urbach). Carnot and Slavu were also able to confirm this in animal experiments. They showed that oral administration of 3 per cent hydrochloric acid will prevent anaphylaxis from ingested weakly antigenic proteins (e.g., horse serum). It should be emphasized that the management of these secretory disturbances generally requires relatively large quantities of hydrochloric acid in combination with pepsin, as in the following prescription:

		Gm or Cc	
R	Dilute hydrochloric acid		
	Pepsin	āā 120	āā 5 m
	Distilled water	qs ad 1200	qs ad 5 iv
M Sig 1 tablespoonful in ½ glass of water at every meal			

Oelgoetz and his associates,²⁴ Bradley and Belfer,²⁵ and others pointed out that food allergies may sometimes be dependent upon pancreatic hypofunction. As an example of food allergy based on this mechanism, we cite the case of Nathan,²⁶ that of a child hypersensitive to eggs, with a clinical picture of erythema and diarrhea. The stool was found to have a high content of neutral fat and of poorly digested muscle fibers. During the period of treatment with pancreatin, eggs were tolerated; the allergic symptoms recurred when the pancreatin was stopped. Shushan²⁷ reported a case of gastro-intestinal and allergic

²² W. ALZER, A. and W. ALZER, *M. J. Allergy* 6: 537, 1933

²³ BRAY, G. W. *Quart. J. Med.* 24: 181, 1931

²⁴ OELGOETZ, A. W., OELGOETZ, P. A., and WETTERSD, J. *J. Clin. Med. & Surg.* 47: 152, 1940

²⁵ BRADLEY, H. C., and BELFER, S. *Am. J. Digest. Dis. & Nutrition* 5: 139, 1939

²⁶ NATHAN, M. *Bull. méd., Paris*, 31: 59, 1929

²⁷ SHUSHAN, M. *Rev. Gastroenterol.* 9: 350, 1942

symptoms (flatulence, abdominal pain, nausea, vomiting, belching, periodic episodes of diarrhea, sneezing, rhinopathy, urticaria) due to certain foods. Cure was effected when pancreatic insufficiency was detected and pancreatin instituted. The writers also have repeatedly observed the efficacy of pancreatin (administered preferably in combination with hydrochloric acid and pepsin) in cases of intestinal allergy—even in those in which there was no special evidence of a marked pancreatic insufficiency, such as fatty stools.

Inflammation of the gastric or intestinal mucosa can greatly facilitate the resorption of undigested or of inadequately digested food proteins. Hettwer and Kriz²²⁹ demonstrated this in animal experiments by showing that horse serum introduced into the unligated intestine was absorbed in an undigested state, provided that a local chemical irritation was produced by the addition of small amounts of sodium fluoride. In human beings, the inflammation can be caused by enteritis or colitis. In this connection, along with Shay, Gershon Cohen, and Fels,²³⁰ and Gutzeit,¹⁸⁶ we wish to call special attention to the importance of diseases of the small intestine as a predisposing factor. According to White,²³¹ infants with colic subsequently develop infantile dermatitis about three times as frequently as do normal babies.

Chronic indulgence in alcohol and highly spiced foods can also cause inflammation of the intestinal mucosa. Hajos found that he could allergize guinea pigs to certain proteins only if he administered cognac at the same time. Van Leeuwen and the senior author have observed cases in which hypersensitiveness to particular foods manifested itself only when champagne, wine, or onions were taken at the same time. Gutmann²³² stresses the point that coffee, tea, spinach, and other items of food can pave the way for an allergy, in that they tend to increase the permeability of the mucosa. Furthermore, Lortat Jacob²³³ believes that gastric or intestinal erosions or ulcers facilitate the absorption of food proteins into the blood stream.

Finally, we should point to the importance of chronic constipation, as well as of intestinal atony, as predisposing factors. It is not yet generally recognized how frequently allergization can be brought on by the resulting alteration of the food proteins—along with the subsequent presence of pathologic intestinal flora. In animal experiments, Hettwer and Kriz²²⁹ have demonstrated an increase in protein absorption following a rise in intra intestinal pressure due to stasis. They injected horse serum into a temporarily isolated loop of a guinea pig intestine and were subsequently able to elicit anaphylactic manifestations by means of oral and rectal administration of the serum. This result could not be achieved if the serum was originally injected intraperitoneally.

E. HEPATIC DYSFUNCTION

One of the many important functions of the liver is to serve as a filter and detoxifying organ. It is a known fact that the liver, by means of conjugation and catabolic processes, is capable of converting such partially digested proteins as have passed through the intestinal wall into products from which the body's own protein can be formed. Dujardin and Decamps²³⁴ and others have shown, however, that excessive amounts of protein will cause even a healthy liver to lose its normal proteoxygenic function, so that foreign protein enters the circulation with subsequent allergization. The results are similar when, owing to disease or functional disturbances, the liver fails to act as a filter of protein. A Pick and E. P. Pick²³⁵ were the first to describe clinically the importance of hepatic insufficiency in the production of enteric allergization. This was then confirmed by Yoshiyuki's²³⁶ precise experimental findings. In this connection, one must bear in mind the good results obtained in severe cases of dermatitis, urticaria, and other diseases, with such therapeutic measures as systematic gallbladder drainage by means of the duodenal tube, stimulation of the flow of gall by administration of magnesium sulfate

²²⁹ HETTWER J. P. and KRIZ R. A. *Am. J. Physiol.* 73: 539 1925
²³⁰ SHAY H. GERSHON COHEN J. and FELS S. S. *Ann. Int. Med.* 13: 294 1939

²³¹ WHITE P. *Am. J. Dis. Child.* 38: 935 1929

²³² GUTMANN M. J. *Muenchen med. Wochenschr.* 80: 258 1933

²³³ LORTAT JACOB L. *Presse med.* 33: 1679 1925

²³⁴ DUJARDIN B. and DECAMPS N. *Ann. de dermat. et syph.* 6: 725 1925

²³⁵ PICK E. P. *Wien med. Wochenschr.* 63: 315 1913

²³⁶ YOSHIYUKI H. *Scient. Rep. Gov. Inst. Infect. Dis. (Tokyo Imp. Univ.)* 1922: vol. 1

(Smithies²⁴⁷), intravenous decholin (Shay, Gershon-Cohen, and Fels²⁴⁸), or a combined insulin and high carbohydrate regimen (Urbach²⁴⁹).

Obviously, one must make sure that in the case under consideration the liver disease is the cause of the allergic manifestations, and that icterus, for example, is not due to an allergic urticarial swelling of the common duct. Further, one must always consider the possibility that both the urticaria and the liver damage may be coordinate symptoms of a common, perhaps allergic, noxa (as in the case of Ferrabouc and Jude²⁵⁰ in which ingestion of fish was followed by urticaria, angioneurotic edema, arthralgia, and icterus). Mention might also be made of a case reported by Flandin and Vallery-Radot,²⁵¹ in which a second injection of tetanus serum was followed by urticaria, fever, and jaundice. Furthermore, as Manwaring,²⁵² Barber,¹⁵² and the senior writer have pointed out, a liver that has been damaged by infection or intoxication can produce substances that may assume the character of antigens. These antigens can be considered, therefore, as being endogenous (see p. 118).

Finally, liver disease can bring on allergization in still another manner—namely, when the liver pathologically produces porphyrin, a substance that induces a state of hypersensitiveness to light. (For a discussion of porphyrin, see p. 420).

F. INFECTION, INFESTATION, AND INTOXICATION

The rôle played by micro-organisms in calling forth the basic mechanisms of allergization cannot be overestimated. It can be assumed that the bacteria or their toxins lower the threshold of tolerance to the antigen. Both acute infectious diseases and chronic foci of infection are to be considered in this regard. It is unnecessary to dwell on the importance of acute respiratory infections

(coryza, tracheitis, bronchitis, pneumonia) in the onset of allergic rhinopathies and asthma. But it must be remembered that whooping cough, diphtheria, measles, scarlet fever, phlegmons, and erysipelas can also be predisposing factors of prime importance. Two citations will exemplify this. Koenigsfeld²⁵³ reported observing in himself hypersensitiveness to amidopyrine, with a clinical picture of asthma, manifested only during the course of a grippé; the drug was well tolerated at all other times. The senior author succeeded in demonstrating the importance of staphylococcal infection as a predisposing factor by noting that several subjects used as recipients in Prausnitz-Kuestner tests were systemically allergized when suffering from furunculosis.

The local influence of infection is shown by another case (Urbach²⁵³), that of a woman who had had an extensive phlegmon on one leg, and in whom the oral administration of quinine produced an exanthem confined to this previously infected area. A similar case is reported by Naegeli²⁵⁴: a female epileptic, who had tolerated bromide for years, presented a bromoderma on the forearm following an abscess in this area. The predisposing rôle of acute infections has also been confirmed by animal experiments (Bieling,¹⁵⁹ Cormia²⁵⁵).

It is in the very nature of acute infections that their allergizing influence is limited to a relatively brief period of time. Quite the opposite is true, however, of the so-called focal infections. The latter term connotes that a circumscribed focus of infection exerts a distant effect of some sort by means of hematogenous or lymphogenous distribution of bacteria or bacterial toxins; this may result in diseases of individual organs or even of the entire organism—often predisposing to allergization (Rosenow).

It will be seen from Table 11 that only systematic and thorough investigation, often requiring the services of specialists in various fields, will disclose a focus of infection in a given case. It is often extraordinarily difficult to determine, for example, whether or not an existing dental granuloma has any etiologic

²⁴⁷ SMITHIES, F. *Ann Int Med* 3: 1205, 1930

²⁴⁸ SHAY, H., GERSHON COHEN, J., and FELS, S. S. *Am J Digest Dis & Nutrition* 6: 345, 1939

²⁴⁹ URBACH, E., and LEWIS, E. B. *Skin Diseases, Nutrition and Metabolism*. New York: Grune & Stratton, 1946

²⁵⁰ FERRABOUC, L., and JUDE, A. *Bull etimée Soc med d hop de Paris* 51: 727, 1935

²⁵¹ FLANDIN, C., and VALLERY RADOT, P. *ibid* 45, 1072, 1931

²⁵² MANWARING, W. H., ET AL. *J Immunol* 19: 63, 357, 1927

²⁵³ URBACH, E. *Arch f Dermat u Syph* 148, 146, 1924

²⁵⁴ NAEGLI, O. *Klin Wochschr* 4, 25, 1927

²⁵⁵ CORMIA, F. E. *J Invest Dermat* 1: 199, 1933

connection with an allergic rhinopathy. An uncritical attitude regarding surgery must be avoided, as must also a pessimistic resignation to inaction. The problem of the etiologic significance of a focus of infection can best be answered in an individual case by conscientious clinical observation, by attempts to elicit the allergic response by stirring up the infection, and/or by provoking flare ups of the allergic manifestations by means of the administration of autogenous vaccines.

is to be especially directed to dead teeth with canals that have either not been filled or in which the fillings do not reach the apical foramina, to loose teeth or those with large fillings, pegs, and bridgework, to crowned teeth, and to retained roots.

Two of our cases may serve as illustrations. One was that of a young woman who presented an extensive acute dermatitis (Fig. 11) after taking 0.5 Gm ($\frac{1}{2}$ grains) of acetylsalicylic acid to alleviate toothache. When the skin

TABLE II — Important Sites of Focal Infection

Site	Form of Infection	Site	Form of Infection
Eyes	dacryocystitis		
Ears	infection of external auditory canal otitis media mastoiditis	Gastro intestinal tract	gastro enteritis appendicitis colitis proctitis dysbacteria (abnormal intestinal flora)
Paranasal sinuses	frontal sinusitis maxillary sinusitis ethmoiditis sphenoiditis	Gallbladder	cholecystitis
		Urinary tract	pyelonephritis cystitis urethritis
Teeth	pyorrhea alveolaris periodontal pocket periodontitis retained roots alveolar abscess periapical infection dead tooth granuloma cyst suppurating pulpitis osteitis	Genitalia	prostatitis vesiculitis endometritis salpingitis oophoritis endocervicitis
		Bones and joints	osteomyelitis infectious arthritis
Bronchi	bronchitis bronchiectasis	Skin	pyoderma paronychia (fingers toes) fungus infection

As regards possible dental focal infection, it must be remembered that mere roentgenographic investigation is not sufficient. Alterations in the response to tapping, determination of pulp sensitivity to thermal and electric stimuli, examination as to whether the regional submaxillary lymph nodes are enlarged and even slightly tender (G. Stein), and bacteriologic investigation of the foci by aerobic and anaerobic cultures are some of the important approaches that have to be considered by the dental consultant. On principle, suspicion

condition had cleared, the administration of the same dose of acetylsalicylic acid was followed by a reappearance of the bullous eruption. Dental examination revealed an acute pulpitis. Several days after the toothache had subsided, the drug was twice administered, with negative results both times. Figure 12 shows a papular urticaria of several weeks' duration in another patient. The skin condition flared up after ingestion of egg and incision of a periostitis, this food was tolerated, however, after removal of an infected tooth

Moncorps has reported an observation in himself of an angioneurotic edema due to hypersensitiveness to certain drinks and foods, with disappearance of the cutaneous response

it shows no local symptoms whatsoever—namely, pathologic flora of the intestines, especially of the colon. The so-called colon dysbacteria (so named by Nissle) is character-



FIG. 11 FOCAL INFECTION AS PREDISPOSING FACTOR IN ALLERGIZATION
Acute dermatitis due to ingestion of acetylsalicylic acid during acute dental infection



FIG. 12 FOCAL INFECTION AS PREDISPOSING FACTOR IN ALLERGIZATION

Exacerbation of papular urticaria due to egg, following incision of periodontitis. After extraction of infected tooth, eggs could be eaten without effect

after resection of two apical granulomata and treatment of an existing periodontitis

Numerous examples of the importance of general and focal infections will be given in Parts Two and Three, with reference to the individual allergic diseases. We shall here merely mention one form of focal infection that has received only scant attention, since

ized by a replacement of the normal colonic flora by streptococci and by atypical, biologically inferior colon bacilli. This condition can be demonstrated only by bacteriologic study of the stool by means of appropriate aerobic and anaerobic cultures. Thus, Nissle²⁵⁴ reports the case of a woman suffering

²⁵⁴ NISSE, A. *München med Wchnschr* 83: 1793, 1936.

from constipation and urticaria due to straw berries and fish. The stool revealed a colon dysbacteria. Therapy consisting of oral administration of living colon bacilli (Mutaflor) resulted in the complete replacement of the pathologic intestinal flora by normal organisms, with relief of the constipation and disappearance of the urticarial response to the foods in question. The writers have seen similar results quite frequently.

In addition to the pathogenic microorganisms, the saprophytic bacteria can also act as predisposing factors. Sabouraud⁵⁷ has long insisted that the normal bacterial flora of the skin plays a part in the production and maintenance of certain dermatitides. These clinical observations were recently confirmed by Haxthausen, who produced cutaneous sensitization by adding a suspension of staphylococci cultured from normal skin to mercuric chloride, chromic acid, formalin and other chemicals. Without some such conjugation these chemicals rarely act as antigens.

The contributory role of fungus infection of the skin—as by trichophyton, monilia and other fungi—in the production of hypersensitiveness to other agents was especially emphasized by Stokes and Garner.²¹⁴ This mechanism is of great practical importance. Thus, Stokes and Kulchar²¹⁵ have shown that arsphenamine may be well tolerated until a fungus infection supervenes. It has been demonstrated that fungus infection predisposes to allergic contact dermatitis from leather (Beerman²¹⁶) from occupational agents such as cake flour, cottonseed oil silk (White and Taub²¹⁷), and from sock dye and shoe polish (Wise and Sulzberger²¹⁸). In experiments on human beings, Haxthausen²¹⁹ showed that a definitely allergic state could be produced by mixing a yeast suspension (obtained from a culture from a case of intertrigo) with bichloride of mercury (1:1,000), which alone is unable to cause allergization. Peck, Bot-

winick, and Schwartz,²²⁰ however, deny that fungous infection or dermatophytids constitute predisposing factors in allergic contact dermatitis, except in so far as the resulting open lesions, like those due to any cause, even trauma may offer an easy entrance for external irritants. In a group of workers studied by them 42 per cent gave positive trichophyton reactions, but only an estimated 0.2 per cent had allergic contact dermatitis. Moreover, only three cases of 'ids' of the hands were discovered in over 2000 workers examined.

Finally, the fact is to be stressed that local infections, like trauma can be instrumental in localizing a specific allergic process to a given organ, such as the eye. This is called by Riehm "elective sensitization." In cases of long standing infection the resultant allergic state cannot usually be removed by merely eliminating the infection. Similarly, when skin tests to the bacterial agent have become positive, removal of the infection will not readily alter the reactivity of the skin to the bacteria (for detailed discussion, see p. 436).

We must also mention briefly the importance of infestation as a predisposing factor. In children especially, but also in adults living in hot climates, the rôle played by infestations is generally underestimated. Intestinal parasites (e.g., oxyurias, ascariides, tapeworms, echinococci) are chiefly to be considered. Thus Kerl reported a severe case of cold urticaria that was cured only after extermination of an ascaris infestation. Adelsberger and Munter described the case of a young woman with severe dermatitis whose skin condition cleared up after elimination of certain foods from her diet, but reappeared when she failed to adhere to the regimen. After successful treatment of a tapeworm infestation, however the patient's intolerance disappeared completely.

Toxic states finally, can also pave the way for allergies. In this category belong those hypersensitivities that follow poisoning by drugs such as arsphenamine, gold, and mercury, or that are initiated by poisonous insect bites. In this connection, alcohol and nicotine must also be mentioned since excessive use of them

⁵⁷ SABOURAUD R. Eighth Internat. Cong. Dermat. & Syph. Copenhagen 1930 p. 131.

²¹⁴ STOKES J. H. and KULCHAR G. V. *Brit. J. Dermat.* 46: 133 1934.

²¹⁵ BEERMAN H. *Arch. Dermat. & Syph.* 29: 671 1934.

²¹⁶ WHITE C. and TAUB S. J. *J. A. M. A.* 98: 524 1932.

²¹⁷ WISE F. and SULZBERGER M. B. *Yr. Bk. Dermat. & Syph.* 1934 p. 86.

²¹⁸ HAXTHAUSEN H. *Acta dermat. venerol.* 17: 275 1936.

²²⁰ PECK S. M., BOTWINICK I. and SCHWARTZ L. *Arch. Dermat. & Syph.* 53: 173 1941.

keeps the vascular system and the autonomic nervous system in a chronic state of irritability.

G. NUTRITION

We are probably not yet fully aware of the importance of defective diets in predisposing to an allergic state in relation to other allergens. By this we do not refer to the well-known food allergies. We shall here disregard certain factors that are important in individual cases but do not concern the general problem involved: among these are faulty mastication, which is often due to missing teeth, inadequate salivation, hasty swallowing of foods (a result of the hectic tempo of present-day life), overly rich foods, etc. Our discussion will be limited to those basic points that show that the diet of the so-called civilized peoples has undergone a considerable qualitative change. These are as follows:

(1) The constantly increasing use of chemical fertilizers has changed the chemical composition of vegetables, fruits, and animal fodder, in the direction of an increased content of potassium, iodine, and other elements. For example, as Sulzberger points out, carrots grown in one place without artificial fertilizer contain 19 parts of iodine per 1,000,000, while carrots grown with artificial fertilizer contain 2,100 parts. It is not at all inconceivable that such changes in the chemical composition of foodstuffs may lead to increased sensitization.

(2) The wider consumption of canned foods means that increasing amounts of chemicals added as preservatives (e.g., sodium benzoate, salicylic acid, and sodium chloride) are ingested; besides this, traces of metal—small as they may be—find their way into the body.

(3) Countless people take iodized salt. Iodine, of course, by reason of its influence on the thyroid gland, represents a possible predisposing cause of allergization. Bechet²⁶ suggested that the ingestion of iodized salt may sensitize patients to such a degree that subsequent small medicinal doses of iodides may cause severe iododermas and possibly even death.

(4) The drinking water of our large cities has a high chlorine content.

(5) Flour contains considerable quantities of potassium and ammonium persulfate; these chemicals, added for the purpose of bleaching the flour and of making it easier to bake, are also likely to allergize (p. 405).

(6) Increased use of chemicals in combating pests in orchards, fields, and vineyards results in a constant increase in the quantities of arsenic and other poisons to be found in fruits, vegetables, wines, etc.

(7) The typical inhabitant of a large city is likely to eat highly salted and spiced foods, thus exposing himself to irritation of the intestinal mucosa.

(8) He is also likely to consume far too much protein, especially animal protein (meat, eggs).

(9) Generally speaking, our cooked foods are deficient in vitamin content.

(10) In certain areas—of South Dakota, for example, and of Nebraska and Wyoming—wheat, corn, and barley grow on soil that contains enough selenium to bring on the so-called "alkali disease" in animals. Investigative studies have yet to be undertaken to determine whether selenium—a "chemical cousin" of sulfur—exerts a sensitizing influence other than its known toxic effect.

Aside from these factors that affect the diet of a great part of the population, there are others of equal importance. Thus, as Luthlen's²⁸ fundamental investigations have shown, an acidotic diet tends to decrease the resistance of the organism and especially of the skin, an alkalotic diet, on the other hand, tends to increase resistance. Klauder and Brown²⁶ continued investigation along these lines, and found that the winter diet of animals (oats, bread, etc.) is an acidotic diet tending to increase susceptibility to sensitization; while the summer diet (green fodder) is alkalotic, and definitely decreases the animal's susceptibility to sensitization. These findings were confirmed by experiments performed by Sulzberger and Mayer²⁷: animals could not be allergized to arsphenamine, for example, during the summer when they were on an alkalotic diet, but they could be when on a

²⁶ L. LUTHLEN, F. *Pharmakologie der Haut*. Berlin: Springer, 1921.
²⁷ KLAUDER, J. V., and BROWN, H. *Arch. Dermat. & Syph.* 11: 283, 1923.
²⁸ SULZBERGER, M. B., and MAYER, R. L. *ibid.* 21: 337, 1931.

winter diet (acidotic), and vice versa. Von Engel was able to demonstrate that animals on a winter diet gave tuberculin reactions that were stronger than those given by animals on a summer diet. It is quite possible that much of the effect of these dietary regimens depended on differences in their vitamin content rather than on other qualities.

Koenigstein reported an interesting observation: a salt poor diet increases the susceptibility of the skin to allergization. This was confirmed by Kile and Pepple,²⁶⁵ who showed that sensitized animals on a salt free diet gave more marked allergic reactions than the controls. Gerson came to the same conclusion in regard to human beings. He observed that tuberculous individuals subsisting on a salt poor diet gave very strong and occasionally alarming reactions to tuberculin. According to Bremner a low salt diet increases the sensitivity of the skin to ultraviolet rays.

Despite a great deal of experimental work on the subject, the question of whether or not vitamin deficiency influences the susceptibility of the organism to allergization remains a highly controversial point. On the one hand, Sulzberger and Oser,²⁶⁶ Cormia,²⁷⁰ and Streitmenn, Wiedmann, Hochwald, Diehl, and others maintain that animals on a diet deficient in vitamins can be sensitized more readily than animals on a diet containing adequate amounts of vitamin C. These authors found that it was impossible to produce sensitization to arsphenamine in guinea pigs after a period of high vitamin C intake. As early as 1924, Wedgewood²⁷² showed that lethal anaphylaxis in guinea pigs could be completely prevented by injections of lemon juice. McClesney et al.²⁷³ found that ascorbic, isoascorbic, and d-glucoscorbic acids as well as lactic acid, reduced the toxicity of arsenicals in animals provided they are administered in adequate dosage and at the same time

Bertellotti²⁷⁴ showed that a state of vitamin C deficiency lowered the minimal lethal dose of arsphenamine in animals while tolerance could be restored to normal by adding synthetic vitamin C to the diet. Similarly Steimbach and Kiern²⁷⁵ demonstrated that cevitamic acid increased the tolerance of the animals to tuberculin. A partial degree of protection against anaphylaxis requiring large dosage of ascorbic acid administered simultaneously with or shortly before the sensitizing dose, was reported by Pacheco and Para²⁷⁶. Farmer and Kassman²⁷⁷ believe that if vitamin deficiency is carried to the point of depletion of the ascorbic stores of the adrenals anaphylaxis is enhanced. Lesser degrees have no effect on anaphylaxis, but suffice to increase lethal shock from histamine, as compared with control animals. These effects are attributed²⁷⁸ to a decrease in the cholesterol content of the adrenals, leading to a diminution in the content of cortical hormone. On the other hand certain authors including Cohen,²⁷⁹ and McDonald and Johnson,²⁸⁰ found that neither deficiency nor overdose of vitamin C had an effect on eczematogenous sensitization to arsphenamine or to poison ivy and no influence on anaphylactic shock. Similar frankly negative reports were made by Dragstedt et al.²⁸¹, Fuller et al.²⁸² and others. And Kile and Pepple²⁶⁵ went so far as to state that animals placed on a diet free of vitamin C until they showed marked symptoms of avitaminosis could not be sensitized. These discrepancies may possibly be explained in the light of Yoshikawa's²⁸³ observations that the daily administration of small quantities (25 mg) of vitamin C while guinea pigs are being allergized, will increase the allergy, moderate

* BERTELLOTTI L. *Minerva med.* 30: 254 1939

265 KILE R. L. and PEPPLE A. W. *J. Invest. Dermat.* 1: 59 1938

266 SULZBERGER M. B. and OSER B. L. *Proc. Soc. Exper. Biol. & Med.* 35: 151 1936

267 PACHECO G. and PARA M. *Compt. rend. Soc. de Biol.* 129: 419 1938

268 FARMER L. and KASSMAN S. R. *Am. J. Clin. Path.* 13: 362 1943

269 FARMER L. *ibid.* 13: 355 1943

270 COHEN M. B. *J. Allergy* 10: 15 1938

271 McDONALD F. M. and JOHNSON H. H. *Arch. Dermat. & Syph.* 43: 682 1941

272 WEDGEWOOD P. E. *Univ. Cincinnati Med. Bull.* 2: 1 1924

273 FULLER A. E., ROBERTS L. B., RALLI E. P. and FRANCIS T. *J. Clin. Invest.* 21: 121 1942

274 YOSHIKAWA K. *Nagasaki Igakkai Zasshi* 17: 165 1939

265 KILE R. L. and PEPPLE A. W. *J. Invest. Dermat.* 1: 59 1938

266 SULZBERGER M. B. and OSER B. L. *Proc. Soc. Exper. Biol. & Med.* 32: 16 1935

267 CORMIA F. E. *Canad. M. A. J.* 36: 372 1933

268 Idem. *J. Invest. Dermat.* 4: 81 1941

269 WEDGEWOOD P. E. *Univ. Cincinnati Med. Bull.* 2: 1 1924

270 MCCLESNEY E. W., BARLOW O. W. and KLENCK G. H. Jr. *J. Pharmacol. & Exper. Therap.* 80: 85 1944

doses will have no effect, and large doses (100 mg.) will have an inhibiting influence.

Reports of attempts to influence human allergies by means of vitamin C are equally controversial (Bundeson et al.²⁸⁴). Partial or complete avoidance of sensitivity to arspenamine by means of ascorbic acid was reported by Dainow,²⁸⁵ to sulfonamides by Pelner²⁸⁶ and Schropp,²⁸⁷ and to salicylates by Pelner.²⁸⁸ Beneficial results in various allergic diseases from large doses of vitamin C were reported by Holmes and Alexander,²⁸⁹ Holmes,²⁹⁰ Rosenberg,²⁹¹ Hagiescu et al.,²⁹² and others. However, the bulk of recent reports (Hunt,²⁹³ Hebalde,²⁹⁴ Engelsber,²⁹⁵ Friedlaender and Feinberg,²⁹⁶ Lieder,²⁹⁷ and others) are entirely unfavorable to this therapy. The observations of the present authors are in complete agreement. Newbold²⁹⁸ found that ascorbic acid had no significant effect on skin reactions to intradermal pollen testing in hay fever cases.

A résumé of the recent investigations on this problem was included in a review of the relationship of vitamins to allergy by Brown.²⁹⁹

The entire question evidently requires further study by technics that avoid the uncertainties inherent in most or all of the investigations cited above. Certainly one important reason for the discrepancies lies in the failure clearly to differentiate between allergization and non-allergic toxicity (since ascorbic acid does appear to have a detoxifying effect on pentavalent arsenical compounds). Moreover, a careful appraisal of the state of vitamin C balance both in experimental animals and in human subjects employed in such studies

might partially clarify the difficulties, at least to the extent of determining whether a hypovitaminosis C is being treated.

Yamamoto³⁰⁰ and Kin and Lee³⁰¹ claim that the administration of vitamin B₁ during allergization, or prior to administration of the shock dose, has an inhibiting effect on anaphylactic shock in guinea pigs. According to Wedgewood and Grant, the rat can be allergized only when on a diet deficient in vitamin B. However, Frei³⁰² found no effect of vitamin B complex on anaphylaxis in guinea pigs. Attempts to influence human allergies by administration of thiamin chloride, nicotinic acid, and other factors of the B complex has led to similarly contradictory results (Brown²⁹⁹). Vitamins A and D do not appear to modify either arspenamine sensitization or reaction in guinea pigs (Frei³⁰²).

H SEASONAL, METEOROLOGIC, AND GEOGRAPHIC INFLUENCES

Clinically it is a well-known fact that seasonal, meteorologic, and climatic influences are important factors in the production of allergic diseases and also in the elicitation of individual attacks.

The seasonal influence on the human and animal body is clearly manifested by the fact that in the spring and in the autumn the organism's resistance is lowered, or, in other words, sensitiveness is increased. We shall not discuss seasonal fluctuations in infectious diseases, but shall consider only their effect on allergic diseases and allergic reactivity. Mayer and Cajkovic, and also Koehn, have presented interesting statistics on the seasonal dependency of allergic dermatitides, neurodermatitides, and prurigo. These statistics all show a definite peak reached during the spring and autumn. Peyrer, as well as Schnippenkoetter, have described the occurrence of seasonal trends in the tuberculin reaction, the former author in relation to children, the latter in relation to adults with tuberculosis. They agree on a late spring peak in sensitivity to tuberculin, with smaller skin reactions during the winter months.

The exact reason for this seasonal influence

²⁸⁴ BUNDSESON, H. N., ARON, H. C. S., GREENBAUM, R. S., FARMER, C. J., and ART, A. F. *J. A.M.A.* 117, 1697, 1941.

²⁸⁵ DAINOW, J. *Presse méd.* 45: 1650, 1937.

²⁸⁶ PELNER, L. *New York State J. Med.* 43: 1874, 1943.

²⁸⁷ SCHROPP, J. H. *Canad. M. A. J.* 49: 515, 1943.

²⁸⁸ PELNER, L. *J. Lab. & Clin. Med.* 28: 28, 1942.

²⁸⁹ HOLMES, H. N., and ALEXANDER, W. *Science* 96: 497, 1942.

²⁹⁰ HOLMES, H. N. *Ann. Allergy* 1, 235, 1943.

²⁹¹ ROSENBERG, W. A. *Arch. Dermat. & Syph.* 37: 1019, 1938.

²⁹² HAGIESCU, D., GRISCOLA, M., BAZIAN, G., and CIORANESCU, M. *Presse méd.* 46: 1435, 1938.

²⁹³ HUNT, H. B. *Brit. M. J.* 1: 726, 1938.

²⁹⁴ HEBALD, S. J. *Allergy* 15: 236, 1944.

²⁹⁵ ENGELSBER, D. L. *J.A.M.A.* 126: 318, 1944.

²⁹⁶ FRIEDLAENDER, S., and FEINBERG, S. M. *J. Allergy* 16: 140, 1945.

²⁹⁷ LIEDER, L. E. *Lettres, Internat. Conf. Club of Allergy*, 1943.

²⁹⁸ NEWBOLD, H. L. *J. Allergy* 15: 385, 1944.

²⁹⁹ BROWN, E. A. *Ann. Allergy* 2: 456, 1944.

³⁰⁰ YAMAMOTO, M. *Oriental J. Dis. Infants* 21: 11, 1938.

³⁰¹ KIN, S. S., and LEE, H. K. *J. Chosen M. A.* 29: 21, 1939.

³⁰² FREI, W. *J. Invest. Dermat.* 5: 117, 1942.

is not known. Various possibilities have been advanced, including endocrine factors, changes in the composition of foods (winter and summer diets, as mentioned above), and other mechanisms.

Petersen and Milliken³⁰³ and De Rudder³⁰¹ compiled numerous observations on the connection between the weather and asthma. As is well known, many patients with asthma, rhinopathy, and migraine suffer particularly severe attacks on sudden changes in the weather. Kaemmerer³⁰⁵ reported a definite relationship between chronic urticaria and certain weather conditions. More recent investigations have demonstrated the importance of meteorologic and atmospheric conditions, such as barometric pressure, air motion, temperature, high humidity, degree and duration of sunshine, atmospheric electricity, etc. Years ago, Hansen and Michenfelder observed, in the course of allergy testing in human beings, that the reactions were stronger when the barometer was low than when it was high. Likewise, Courtright and Courtright³⁰⁶ showed that an experimental condition of low atmospheric pressure was conducive to a significantly higher number of reactions in guinea pig anaphylaxis than was high pressure. Both Lauf and Haag demonstrated by means of animal experiments that a rise in atmospheric pressure tends to inhibit anaphylactic shock, while a decrease in air pressure has little effect, and that the decisive factor is not the level of the pressure but rather its fluctuations. According to Preuner,³¹¹ the susceptibility to attack in allergized animals depends not so much on individual meteorologic factors (e.g., atmospheric pressure, temperature, humidity), as on general weather conditions, such as the movements of masses of air, sudden changes of heat and cold fronts, etc. Similarly, Courtright and Courtright³⁰⁶ found that "shifts" in the atmospheric conditions to which guinea pigs were exposed were more favorable to severe anaphylactic reactions

than any single set of conditions, although even the latter had considerable influence. The greatest number of shock reactions occurred on shift (1) from hot dry air to low barometric pressure, (2) from low pressure to hot dry air, and (3) from hot moist to cold dry air without the allergen, and back to hot moist air with the allergen. Petersen and Vaughan³⁰⁷ noted that deaths from asthma occur more frequently following a marked drop in atmospheric temperature (major polar air masses) with exitus during the subsequent rise, often accompanied by a barometric crest. However, other types of weather changes (in humidity, air ionization, wind velocity, etc.) may be significant.

Hagen, Bettmann and others have shown that atmospheric influences bring about objective organic changes. Microscopic observation of the capillaries reveals that the vascular system undergoes abnormally exaggerated reactions (spasm, paralysis) following thunderstorms or sudden changes in weather. Petersen³⁰³ has pointed out that vasoconstriction and vasodilatation, reflected in blood pressure readings, are largely influenced by the meteorologic environment, particularly by the infall of polar air, which causes peripheral vasoconstriction. Weather changes also have a profound effect on the autonomic nervous system, endocrine mechanism, chemical balance (blood pH, K/Ca ratio, protein concentration, etc.), and even in variations in tolerance of drugs, including opiates (Petersen and Vaughan³⁰⁷). Resulting local tissue changes include variations in vascularity, temperature, and fluid balance, in the viscosity, osmotic pressure, and surface tension of the mucus, in ciliary activity, and in the adsorption of the allergen (Courtright and Courtright³⁰⁶). Periods of peripheral vasodilatation characterized by a drop in diastolic blood pressure are accompanied, according to Howe,³⁰⁸ by an increased reaction to tuberculin. Conversely, a decreased tuberculin sensitivity will be found at times of peripheral vasoconstriction, as manifested by a rise in diastolic pressure.

³⁰³ PETERSEN W. F. and MILLIKEN M. E. *The Patient and the Weather*. Ann Arbor Mich. Edwards 1934.

³⁰⁴ RUDDER B. *De Wetter und Jahreszeit als Krankheitsfaktor*. Berlin Springer 1931.

³⁰⁵ KAEMMERER H. *Allergische Diathese und allergische Erkrankungen*. ed 2. Munich Bergmann 1934.

³⁰⁶ COURTRIGHT L. J. and COURTRIGHT A. B. *J. Allergy* 16: 145 1945.

³⁰⁷ PETERSEN W. F. and VAUGHAN W. T. *Ibid* 15: 97 1914.

³⁰⁸ HOWE J. S. *Am Rev Tuberc* 37: 273 1938.

Petersen³⁰⁹ recently reviewed the profound fluctuations in body physiology and the complex interplay of the various "balances" maintaining the equilibrium of the organism, occurring in consonance with seasonal and day-by-day variations in environmental conditions, particularly as regards meteorologic factors. These are of immense importance to the allergist in their influence on reactivity to testing, in evaluating the patient's response to exposure to the allergen, and in understanding other allergic phenomena.

Geographic influences must also be considered. It is well known that the nature of the soil plays a rôle, notably in asthma. Areas situated on the seashore and therefore damp, as well as moors and clay soil, favor development of asthma and rhinopathy, probably because of the presence of great quantities of molds and bacteria. Dry regions (deserts, dunes) are much better for patients with asthma. Furthermore, the type and quantity of vegetation in a given region is of considerable importance. High altitudes are known to be beneficial in alleviation of allergies, owing mainly to the sparse vegetation and to the relative absence of inhalant allergens. Moreover, endocrine influences and metabolic changes occasioned by the high altitude might well play a part, since it has been demonstrated that the threshold of sensitivity is generally higher in the mountains. The senior author observed, for example, a case with manifest hypersensitiveness to trout when the patient was in the city; in the mountains, however, at an altitude of some 2,700 feet, the patient was able to enjoy this fish, prepared in an identical manner, with complete freedom from symptoms. Brandt and the senior author knew a physician who for many years had been hypersensitive to eggs, after several weeks' sojourn in the mountains (at an altitude of 3,000 feet), this hypersensitiveness was no longer manifest, though it reappeared soon after the patient's return to the city. Rowe³¹⁰ recorded the beneficial effect of dry and particularly of high regions on food sensitiveness.

It is apparent that the pollen grains and fungous spores which a patient inhales, the

plants with which he comes into contact, the foods he is likely to eat, and even the type of animal danders to which he is exposed will be indirectly determined in large part by geographic and climatic influences. References to these relationships will be found throughout the other parts of the book.

I. SOCIAL AND ENVIRONMENTAL FACTORS

The allergic diseases are definitely diseases of civilization. Just what is responsible for this is not well known. Among the factors that must be considered are: the increasing artificiality of our diet, faulty diet (increased consumption of protein, salt, and spices, as well as of food substitutes); the hectic tempo, excitement, and tension of city life, central heating and air conditioning; polluted air, due to automobile exhaust fumes, gasoline, dust, etc. Each of these various potential factors has been discussed separately elsewhere, in its appropriate place.

We must not overlook the fact that there is a social factor predisposing to allergy: the intellectually and socially superior classes appear to have a considerably higher incidence of allergies. Thus, 75 per cent of 300 cases of asthma, ranging from 2 to 20 years in age, were above average in scholarship, and only 1 per cent was below (Clarkson³¹¹). It is quite possible, however, that the material in this and similar investigations represented "selected" cases. Certainly, Piness et al.³¹² found the intelligence level of allergic children not to be significantly different from that of controls. Experience in clinics has convinced the writers that allergic patients come from all intellectual, social, and economic strata in about the same proportion as the general population.

The rural population shows much lower incidence of hay fever than does the urban. This may well be explained by the fact that continuous contact tends to produce hypersensitization, while intermittent contact prevents the development of adequate protection. Furthermore, the farmer, since he is not exposed to the psychic and other irritations of city life, is much less likely to be

³¹¹ CLARKSON, A. K. *Brit. M. J.* 2: 845, 1937.

³¹² PINESS, G., MILLER, H., and SULLIVAN, E. B. *J. Allergy* 8: 168, 1957.

³⁰⁹ PETERSEN, W. F. *J. Ann. Allergy* 3: 348, 1945.

³¹⁰ ROWE, A. H. *Food Allergy*. Philadelphia: Lea, 1931.

allergic than the clerk or the factory worker Hyde and Kingsley³ reported that in the examination of 60 000 selectees the prevalence of disqualifying allergic states was constant in many socio economic backgrounds but there was a definitely increased prevalence of severe allergic states in semirural communities and a greatly decreased rate in crowded tenement districts

Among the environmental factors exposure to the allergen is by far the most important It has now been definitely established—by the experimental work of Bloch Landsteiner Sulzberger and others—that allergization depends at least as much on quantitative as on qualitative factors (see p 41) The fundamental experiments of Salen and Juhlin Dannfelt⁴ have shown that subjects whose occupation brings them into especially intimate and very frequent contact with certain substances without producing allergic symptoms have positive skin reactions when tested with them—that is repeated exposures produce a latent allergy These authors found that of 125 bakers 38 per cent gave a positive reaction to rye extract as compared with 5 per cent among controls and further more that in a group of 100 cavalrymen 23 per cent gave positive reactions to horse dander extract as compared to 8 per cent among persons suffering from other allergies The majority of Swedish veterinarians are hypersensitive to brucella antigen Similarly children who live in a tuberculous environment and who show no clinical symptoms manifest a much higher degree of allergy—as demonstrated by their reactions to tuberculin—than do children of the same age who are less intimately exposed to tuberculosis (Pollak) Latent allergies merely require some contributory factor to elicit clinical manifestations One of these factors appears to be a change from continuous to intermittent general or local contact Thus it is not infrequently observed that a worker will present a rather slight local dermatitis as a result of prolonged contact with industrial irritants such as turpentine but severe manifestations will appear only after he has avoided actual contact with the eczematogenous agents for varying periods of time

The factor of exposure must in the future assume an ever increasing importance in predisposition to dermatitides asthma and rhinopathies in view of the tremendously increased contact with chemicals in industry and in the home In addition exposure to pollens molds and smuts is a definite factor in the acquiring of allergic diseases Thus Dutton⁵ found that two seasons of occupational contact with sugar beet pollen was sufficient to allergize an appreciable percentage of workers Phillips⁶ reported that after five seasons of exposure to the spores of the newly identified Johnson grass smut cutaneous and clinical sensitivities to that fungus were widely encountered

J NONSPECIFIC IRRITATION

The reasons why a certain organ or tissue becomes allergized can not infrequently be explained by the fact of a preceding non specific irritation Animal experiments by Seegal and Seegal⁷ demonstrated the importance of nonspecific fixation if glycenn is injected into the anterior chamber of the eye of a specifically sensitized animal the allergic inflammation following the administration of the homologous allergen will be localized to the inflamed uvea

Hansen frequently observed cases of mold asthma becoming manifest only after the patient had been exposed to chlorine vapors which are especially irritating to the bronchial mucosa Other asthmatics have reported that they suffered attacks only after having worked for some time with tar or in occupations that exposed them to smoke Setterstrom has recently claimed that in the course of a single winter day more than 2 000 tons of sulfur dioxide (a gas formed by burning coal) are released into the air in New York City The air over all industrial cities contains tremendous quantities of dust Thus in Chicago a monthly average of 55 2 tons of dust per square mile fell in 1911 This fact will surely help to explain the enormous increase in asthma in industrial cities Other highly important sources of irritation are benzene and oil vapors smoke from chimneys locomotives

³ DEXTON L O J Allergy 9 607 1938

⁴ PHILLIPS E W S d 12 24 1940

⁵ SEEGAL B C and SEEGAL D J Immunol 25 221 1935

and steamships, exhaust fumes from automobiles and factories, and the increasing dust content of the air, due to increased traffic.

We have already discussed (p. 62) the question of nonspecific irritation of the gastrointestinal mucosa—for example, by alcohol, or by highly spiced foods—as a predisposing factor in enteral allergization. We must not forget to include here such irritants as laxatives and “blood-purifying” teas.

Particular importance is assumed by nonspecific irritation in the production of cutaneous allergic diseases. A distinction must be made between acute and chronic irritation. *Acute irritation includes* such trauma as intense sunburn, burns, scalds, and physical injuries, and is not infrequently the pacemaker of local allergic dermatitis, which may subsequently become disseminated. But a far greater rôle is played by chronic irritation, such as friction, repeated minor injuries, chemical influences, particularly of alkalies, and maceration by heat and sweat. Such chronic irritation facilitates epidermal allergization by serving to break down the physical or chemical barriers of the skin, i.e., the horny protective covering of the stratum corneum and the fatty water-repellent sebaceous film that covers the normal skin surface. According to Burckhardt,³¹⁷ the normal skin possesses, as an inherent function of the epidermal cells, the capacity of neutralizing alkaline solutions at a certain rate. He observed the important fact that all dermatitis patients who have been occupationally exposed to the injurious effect of alkalies (e.g., laundresses, galvanizers) exhibit a definitely lowered threshold of resistance to alkali, and that such individuals seem to be prone to allergic sensitization to cement, nickel, and turpentine, in the form of dermatitis. Burckhardt's findings were confirmed by Theiler³¹⁸ and Zingsheim³²² in cases of dermatitis in housewives, lime and cement workers, and employes in laundries and soap factories. In animal experiments, Burckhardt³¹⁷ also showed that the coincident addition of soft soap to an allergen, such as pinene (oil of turpentine), served to intensify the allergization. In this connection, there is interest

in Stauffer's³¹⁹ claim that substances with a high hydrogen ion concentration produce more local sensitization than do those that are nearly neutral.

The importance of nonspecific irritation as a predisposing factor in the development of contact dermatides may be illustrated by several frequently encountered examples. Thus, bakers often develop dermatides on the forearms through the effect of leaven and of subsequent exposure to flour bleaches containing ammonium and potassium persulfate; housewives and laundresses are similarly affected on hands and arms softened by soapy water and exposed to various irritants contained in soap. The predisposing cause in allergic shellac and paint dermatides is generally the use of fat solvents to remove traces of the paint from the skin. All these cases can be explained by the fact that allergization takes place more readily in sites where the skin has been more or less stripped of its protective horny layer as a result of occupational injuries. Acids also exert a harmful influence on the skin.

The danger of allergization is surely being constantly enhanced by the introduction of countless newly discovered chemicals into manufacturing processes. Thus, the American Chemical Society reported that in 1939 alone 25,000 new chemical compounds were perfected. In 1940 the same society recorded the development of more than 1,000 new chemical compounds from nitroparaffin alone, for use as rubber accelerators, insecticides, solvents for lubricating oil, wetting and emulsifying agents, etc. The same progress has continued at an even accelerated rate because of the war.

A seborrheic tendency of the skin, as well as hyperhidrosis, may also be regarded as a nonspecific irritant. Norwood and Evans³²⁰ demonstrated that dermatitis of the hands of workers whose occupation necessitated the wearing of leather gloves, was due to two factors: (1) the macerating effect of the gloves on the perspiring hands, and (2) allergic sensitization due to the occurrence of dermatophytosis elsewhere on the body. Furthermore, it has been frequently observed that allergization due to dyed dresses, blouses,

³¹⁷ BURCKHARDT, W. *Acta dermat. venerol.* 19: 339, 1938

³¹⁹ STAUFFER, H. *Arch. f. Dermat. u. Syph.* 162: 517, 1931

³²⁰ NORWOOD, W. D., and EVANS, E. E. *J. A. M. A.* 114, 1523, 1940

shirts and other garments may arise in the copiously sweating axillary regions. This is to be explained either by the fact that the allergen more readily permeates the softened skin that has lost most of its natural protective sebaceous film or by the fact that the dye by conjugation with the protein content of the sweat assumes the nature of a complete antigen (FIG. 13).

K. PSYCHOSOMATIC RELATIONSHIPS

A steadily accumulating body of evidence indicates the importance of psychic factors in predisposing to precipitating and maintaining allergic diseases. Psychosomatic correla-

or trigger mechanism in an already established allergic disease—essentially a conditioned reflex and (4) as an effect of a chronic or recurrent allergic disease on the personality or psyche of the patient.

It is difficult to state how often apparently allergic conditions may result from purely psychic influences. Among 500 cases of urticaria only 23 could solely be attributed to this etiology (Urbach²²²). Others give differing percentages and certainly they must vary for each disease. Mayer²²³ speaks of psychogenic asthma with the connotation that asthma is only a symptom complex and recommends the psychosomatic approach.



FIG. 13 PERSPIRATION AS A FACTOR PREDISPOSING TO ALLERGY

Postdermatitic pigmentation on a jute mill worker due to hypersensitivity to dye in jute and confined to skin areas that perspire heavily. Finger-like projections are to be noted where sweat carried dyestuff down and patch test with dyed jute was positive only when applied on perspiring skin area.

tions in allergic conditions have been exhaustively presented by Stokes and Beerman²²⁴ and Weiss and English.²¹⁵ The limitations of the psychosomatic approach in allergy and in particular of psychoanalytic thinking on the other hand was considered by Campbell.²²

Psychosomatic influences may stand in any one of four possible relationships to allergy: (1) as the cause of pathergic diseases by essentially psychosomatic mechanisms; (2) as a predisposing factor in the development of allergy—the certain personality constellations and certain psychic situations may pave the way for allergization; (3) as an eliciting factor

Mitchell and Curran²¹⁴ similarly discuss the *nonallergic allergies* in whom ordinary methods of etiologic diagnosis and therapy fail. Such patients reveal an abnormal incidence of complaints of fatigue, exhaustion, headache, gastro-intestinal distress, nail biting, dreams, vague aches and pains, and in children, poor eating habits, thumb sucking, nail biting, and enuresis. These are held to be somatic manifestations of psychological maladjustment in psychoneurotic individuals. Their method of psychotherapy is presented in detail and

²² CURRAH E. Muenchen med. W. hensch. 84: 2054, 1937.

²²³ MAYER S. Jr. Nothwehr Med. 43: 287, 1944.

²²⁴ M. T. HELL, J. H. and C. KRAN, C. C. Midwest Foundation of Allergy.

F. T. Bull. Jan. 21, 1945. Lett. Internat. Club of Allergy, 1945. See #8, p. 43.

consists in substance of repeated nondirected interviews in which the maladjusted patient is encouraged to talk freely and persuaded by degrees to arrive at his own solutions of his problems. By such means, insight is acquired and eventually the patient progresses to independent judgments with resultant decrease of fear and insecurity. Brown and Goitein²²⁹ go so far as to state that sensitivity is "displaced repressed sexuality," and Oberndorf²³⁰ that asthma "is a manifestation of a conflict concerning emission and reception, domination and submission, unconscious masculinity and conscious femininity."

Dekker²²⁷ and Unger²³³ deny the existence of asthma due solely to nervous or psychic stimuli, although granting that they aggravate the frequency and severity of attacks.

The literature reports hundreds of clinical examples proving the importance of psychogenic influences in paving the way for allergies. The renowned French clinician, Trousseau, was himself aware of some such sequence, for he believed that his first asthma attack, due to oat dust in his hayloft, was precipitated only because of a simultaneous psychic excitation (he noticed that his supposedly faithful servant was stealing oats). Kaemmerer observed the case of a young woman who as a girl had never been hypersensitive to eggs; shortly after her marriage she developed asthma elicited only by the ingestion of eggs, and the predisposing factor was discovered to be a severe emotional shock on a sexual basis. Schultz described the case of a mother who was most apprehensively awaiting the outcome of an operation on her child; she then acquired hypersensitiveness to the kind of shrubs that were blooming in the hospital garden at the time of her anxiety.

It is not easy to explain the manner in which psychic factors predispose to allergy. Perhaps the best explanation is that such influences bring on alterations in the excitability of the autonomic nervous system and that stimuli until then of subthreshold level thus acquire the capacity of acting as excitants. Another possibility is that psychic stimuli, by

their effect on the vascular innervation, bring about a change in the blood supply of the peripheral tissues. The result is that pathologic substances that normally cannot penetrate the vessel walls are now absorbed, leading to an antigen-antibody reaction. The psychic factor can also exert its influence by affecting the digestion, either by bringing about a change in the blood supply, motility, or secretions, or by otherwise modifying the functions of the digestive organs. A fourth possibility is that the psychic factor acts in a manner much like the mechanism of the conditioned reflex. Ingenious experiments by Metalnikov²³² of the Pasteur Institute have demonstrated how psychic influences may produce their effects over well-established allergic pathways. Rabbits were immunized intraperitoneally with cholera vibrios, the injections being invariably accompanied by a definite stimulus (e.g., beating of a gong), it was possible eventually to elicit the expected allergic reaction merely by sounding the gong, without administering the antigen.

Mackenzie reports an interesting case that may also be based on a conditioned reflex: a patient with hypersensitiveness to roses always suffered an attack of sneezing at the sight of paper roses. The senior author made a similar observation: a man responded with his typical hay fever symptoms on viewing a scene representing a blooming meadow in the opera *Faust*. It would appear, then, that allergy may become a psychosomatic problem because of the facility with which such reflexes are established. Thus an originally immunologic reaction may become a nervous reaction, especially when associated with apprehensive emotions, and be induced by psychic stimuli.

A relatively constant personality type appears to be characteristic of allergic patients. Rogerson²³⁰ found the asthmatic child to have above-average intelligence, and apt to be irritable, aggressive, quick to respond, over-anxious, insecure, and lacking in self-confidence. Wittkower²³¹ described the allergic personality as one of self-absorption, dreaminess, and ambition. Electroencephalographic

²²⁹ BROWN, E. A., and GOITEIN, P. L. *Psychoanalyst Rev.* 34: 299, 1944.

²³⁰ OBERNDORF, C. P. *New York State J. Med.* 35: 41, 1935.

²³¹ DEKKER, H. *Muenchen med. Wchschr.* 81, 323, 1933.

²³² UNGER, L. *Bronchial Asthma*. Thomas Springfield, 1945.

²³³ METALNIKOV, S. *Rôle du système nerveux et des facteurs biologiques et psychiques dans l'immunité*. Paris: Masson, 1934.

²³⁰ ROGERSON, C. H. *Brit. M. J.* 1: 406, 1943.

²³¹ WITTKOWER, E. *J. Ment. Sc.* 84: 332, 1938.

and personality studies of 45 chronic adult asthmatics by Rubin and Moses³⁷ indicated a single fairly definite personality constellation: fundamentally passive dependent individuals who as children had had an overly protective dominating mother. They had not attempted or attained any great degree of independence in life, and they seek care and protection. Rorschach studies by Ross and McNaughton³⁸ revealed the personality features associated with migraine to be persistence toward success, difficulty in sexual adjustment, perfectionism, inflexibility, conventionality, and intolerance. These had been previously reported in clinical and psychoanalytic studies. Mitchell and Curran³⁹ found some or all of the following characteristics in the maladjusted allergic: an internal state of confusion accompanied by feelings of fear, unhappiness, rejection, and inadequacy, expressions of hostility and guilt, tendency to depend on others, inability to make social adjustment, and seeking to escape by substitute satisfactions or withdrawing into fantasy.

As regards the effect of allergic disease on the psyche, Karnosh⁴⁰ points out that the nervous reactions of allergics are not greatly different from those which follow in the wake of any chronic, irksome, disabling and irritating affliction. The mental attitude is governed by the severity and duration of the disease, colored by the innate personality of the individual. Hence, even though a causative relationship cannot be established, no allergic patient can be adequately evaluated without considering the personality structure in which the disease is implanted. In addition there are the effects of epinephrine and ephedrine on the central nervous system; these are so well known as not to require repetition here. Feinberg⁴¹ states that the asthmatic child may become irritable, nervous, grouchy, or quarrelsome as a result of his disease, or may use his attacks as a basis for gaining sympathy or as a means of escape from onerous duties. He mentions that it is surprising how quickly one can often see a return to completely normal psyche when successful solutions to the allergic

problem have been attained. With this we would emphatically agree. M. Zeller⁴² has reported an increased incidence of alterations of the wave components in the electroencephalograms of allergic patients as compared with nonallergic subjects. These were not present in hay fever. It is interesting to note in this connection that Horneck⁴³ found five times as many neurotic conditions among allergic as among nonallergic persons (20.8 per cent as against 4.4 per cent).

The effect of anxiety, fear and fatigue—due to repeated nocturnal air raid alarms—on the general level of immunity among the people of western Europe, was studied by Pfannenstiel,⁴⁴ using the bactericidal index of blood. He showed that these factors depressed the bactericidal titer very decidedly, leading to markedly lowered resistance to infection.

Recent experimental studies would seem to indicate that the threshold of the allergic reactivity of shock tissue is decreased by psychic factors, and increased if the emotional centers are calmed by hypnosis. Thus Diehl and Heinichen⁴⁵ report that they were able to strengthen or to weaken skin reactions to specific allergens by suggesting to the narcotized patient that the injected allergens were stronger or weaker than was actually the case. Similarly, Clarkson⁴⁶ reported the case of an asthmatic girl with a very strongly positive skin reaction to egg under hypnosis; however, the reaction was negative. The following day, without hypnosis, the skin test was again strongly positive. These observations were confirmed by Marcus and Sahlgren⁴⁷ who succeeded in inhibiting positive reactions to pollen extract by suggesting under hypnosis that the injected allergen was another substance. Not only can an attack of asthma be terminated by hypnosis, but Zeller⁴⁸ has been able to teach asthmatics auto-hypnosis, by which means they can control the attacks at any time without medical attendance. It

³⁷ RUBIN S. and MOSES L. *Psychosom. Med.* 6: 31, 1934.

³⁸ ROSS W. D. and McNAUGHTON F. L. *ibid.* 3: 1935.

³⁹ KARNOSH L. J. *Psychiat. Quart.* 18: 618, 1944.

⁴⁰ FEINBERG S. M. *Allergy in Practice*. Year Book Pub. Co., 1939, 1944.

⁴² ZELLER M. 1934 Regional Congr. Amer. Coll. College of Allergists.

⁴³ HORNECK K. G. *Ztschr. f. menschl. Vererb. u. Konstitutionslehre* 24: 161, 1940.

⁴⁴ PFANNENSTIEL W. and DORTCHER W. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 99: 85, 1940.

⁴⁵ DIEHL F. and HEINICHEN W. *Muenchen med. Wchnschr.* 78: 1008, 1931.

⁴⁶ MARCUS H. and SAHLGREN E. *Acta psychiat. et neurol.* 11: 119, 1936.

must be emphasized that this is by no means a substitute for the usual allergic management. In six of 19 subjects submitting to experimental sensitization of the skin by 2,4-dinitrochlorobenzene, Mom and Noussiton²¹⁰ observed that by non-hypnotic suggestion, such as the use of normal saline in place of the second application of the chemical, the intensity of the reaction could be increased to equal that of the treated areas, and the usual delay in the response eliminated.

Contrary to previous reports, Zeller²¹¹ found that the whealing response of sensitive individuals and that of passive transfer could not be abolished by deep hypnosis, nor could

influence of mental factors such as tension, conflict, fatigue, exhaustion, overwork, rush, disappointment, worry, stress and strain, apprehension, anxiety, fear, grief, sex conflict, etc. In many cases of allergy it is impossible to effect a cure until the mental elements causing disturbance have been eliminated. It has not infrequently been observed that cases of asthma, urticaria, and dermatitis clear up in a hospital environment, where the psychogenic factors are often temporarily removed.

We shall briefly consider whether or not it is proper to employ such terms as "emotional anaphylaxis" (Mairet and Pieron), "allergy to life" (Moschcowitz), or "psycho-allergy"



FIG 14

FIG 15

PSYCHIC INFLUENCE AS PREDISPOSING FACTOR IN ALLERGIZATION

FIG. 14. Angioedematous edema of face, as result of upsetting posthypnotic suggestion.
FIG. 15. Normal appearance of patient

positive reactions be induced in non-sensitized sites.

As a broad generalization, we may state that psychosomatic factors appear to loom the largest in neurodermatitis and urticaria, are of somewhat less importance in asthma and allergic rhinopathy, and of little or no significance in the causation of hay fever and allergic contact dermatitis. Of course, in any disease the patient's reaction to his difficulties will depend on inherent personality traits, and these must be accorded their full value in therapy. Everyone who has dealt with allergic patients is aware of the harmful

(Marshall) If we adhere strictly to our original definition—namely, that every allergy is based on an antigen-antibody mechanism—then we must refuse, at least for the present, to accept these terms, and must substitute the word pathergy. Moschcowitz²¹² answers this objection by emphatically pointing out that in such conditions as infectious allergies and contact dermatitis, antibodies are likewise not demonstrable. "Just as light and heat are nonantigens, so can psychic stimuli be regarded as psychononantigens or psycho-allergens." We should like to say, in reply, that ample proof has been advanced of the allergic nature of infectious allergies and of contact dermatitis

²¹⁰ Mom, A. M., and Noussiton, F. *Rev argent dermatol* 17, 196, 1943.

²¹¹ Zeller, M. *Ann. Allergy* 2: 515, 1944.

²¹² Moschcowitz E. *New England J Med* 213, 617, 1935

There is, of course, the possibility that the same hapten mechanism that seems to be the basis for hypersensitiveness to light and heat (see p. 135) may underlie these cases of allergic symptomatology of psychogenic origin—with the difference, of course, that while an external hapten is operative in the former the hapten, if any, would be of endogenous nature in the latter. The biochemical foundation for this hypothesis is found in the important studies of Lumière³² who showed that emotional shocks bring on chemical changes in the blood in the form of flocculation. This protein can assume the character of foreign protein and can thus become a hapten.

We wonder whether progress of research in the field of endogenous haptens will in the

future explain cases such as the following on the basis of an alteration of the body's own protein due to severe emotional shock. About eight hours after great excitement (usually a football game), a patient observed by Wilder invariably presented an angioneurotic edema of the face and oral mucosa. Under hypnosis he was assigned the posthypnotic task of believing that the football team of which he was such an ardent fan was suffering an overwhelming defeat, eight hours later a swelling set in that was promptly controlled by epinephrine (Figs. 14, 15). We might also mention here the case of a boy who suffered from a severe dermatitis due to hypersensitiveness to caterpillars, after an interval of a year the condition recurred after the boy had been reminded of his illness by merely looking at caterpillars.

³² LUMIÈRE: A. Presse méd. 36: 993, 1928.

CHAPTER V

INCIDENCE OF ALLERGY

IN RECENT years, there has been an alarming increase in the incidence of allergic diseases, even if one conservatively includes as such only asthma, hay fever, rhinopathy, allergic contact dermatitis, and food and drug hypersensitivities. The writers do not believe that this can be explained simply by the theory that physicians are becoming increasingly "allergy conscious." What, then, are the reasons for the well-known fact that in the United States alone there are now millions of hay fever and asthma sufferers, as compared with only some tens of thousands about thirty or forty years ago? Why are they chiefly to be found in the large cities? The various social and environmental factors accounting for this have been discussed in some detail in the preceding chapter.

It is quite difficult to arrive at even a rough estimate of the actual incidence of allergic diseases. Statistics are generally based on the histories and on skin testing. Even granting that one can give credence to a patient's statement that he and members of his family have suffered from asthma, urticaria, migraine, etc., it is now generally accepted that only a portion of such cases may be considered as allergic. And the results of skin tests are even less dependable. When such tests are undertaken with a sufficient number of extracts, it is almost impossible to find an individual who is absolutely "normal." Thus Grow and Herman³² showed that in a group of 150 normal persons tested with thirteen extracts, 55.5 per cent gave positive reactions; of these 150 individuals, 40 gave histories of mild allergic manifestations during childhood, but not of asthma or hay fever. The writers personally are of the opinion that only exposure and elimination tests are reliable for this purpose.

With these limitations in mind, we should like to present some statistics. According to Vaughan, more than 10 per cent of the population present frank allergies, usually of subacute or chronic character—a group that he designates as "major allergics"; approximately 50 per cent give histories of transient episodes

("minor allergics") The difference between the two groups chiefly depends, according to Vaughan, upon the degree and frequency of contact with the offending allergen. These figures would seem to indicate that more than half of all Americans are allergic. Such an interpretation would, however, give an utterly false picture of the general incidence. For, supposing that an individual suffered years ago from urticaria after eating strawberries, or from dermatitis following injections of neoarsphenamine, this does not necessarily mean that he will now react to these allergens. Not everyone who once suffered for several weeks from some gastric or intestinal disorder need now be considered as a gastro-intestinal case. When one counts only the frank allergics and those who show reactions on every adequate exposure to the specific allergen, it will be found that no more than 10 to 20 per cent of the population can be regarded as being truly allergic. Table 12 presents a few of the more important statistical data.

The figures for prevalence of chronic diseases in the United States in 1937, according to the report of the United States Public Health Service,³³ show 3,450,000 cases of hay fever and asthma alone. To these should be added a fair portion (perhaps 25 per cent) of the 1,700,000 cases classified as chronic bronchitis, and of the 1,150,000 cases of sinusitis, since protein and bacterial allergy plays a rather important part in the causation of these diseases. This gives a total incidence for respiratory allergy alone of about 12 per cent of all chronic diseases, or about 3 per cent of the entire population. These figures do not include the millions of sufferers from those forms of hay fever and asthma that are not sufficiently severe or prolonged to cause disability. Moreover, the untold hundreds of thousands of instances of gastro-intestinal, cutaneous, and other allergies, if combined, would give a startling total.

Estimates of the incidence of the individual

³² Preliminary Reports, National Health Survey, Sickness and Medical Care Ser., Bull. 6, U. S. Pub. Health Service, 1934.

allergic diseases also show wide fluctuations. For example, asthma has been found to occur in from 0.5 per cent (Rackemann²⁰) to 3 per cent (Vaughan²¹) of the population groups studied, and hay fever in from 3 per cent (Piness and Miller²²) to 8 per cent (Pipes²³) or 10 per cent (Service²⁴).

The broad experience of the military services and of national selective service examinations has brought out some interesting data. During World War I, 2.62 white soldiers per thousand and 5.6 colored soldiers per thousand were admitted to Army hospitals with a diagnosis of asthma, but 15 years later 12 per thousand were receiving compensation for this disease.²⁵ In 60,000 consecutive examinations of selectees at

diseases (15.7 per thousand) must be allergic. Needless to say, these represent selected groups as regards age and sex.

At one Army post 15.0 cases per thousand required clinic or hospital treatment with rates of 3.41 for hay fever, 2.36 for asthma, 1.31 for perennial rhinitis, 6.32 for various dermatologic allergies, and 1.05 for ophthalmic allergies, according to Blank.²⁶ At a later date, Blank and Levitt²⁷ at the same installation reported that allergic rhinopathy, including hay fever, had an incidence of 6.32 per thousand and men. At another post, Gold and Baze more²⁸ noted a total of 35.01 ambulatory and ward cases of allergy per thousand men with the following rates: asthma 18.0, hay fever 3.9, allergic rhinitis 1.2, "atopic eczema" 3.1, contact dermatitis 0.7, dermatitis venenata 2.5, urticaria and angioneurotic edema 3.1, and migraine 0.3. In both these studies the figures do not reflect the total incidence, since only those soldiers having allergic conditions of sufficient severity to seek or require medical care under military conditions are included. Moreover, in comparison with the findings in the general population surveys given above, these involve only those of military age, nearly exclusively males and a group previously screened by repeated examinations to determine fitness for service.

As to sex distribution, the statistical picture varies with each allergic entity, and further, for any given disease, with the age group. Bray²⁹ concluded from extensive pediatric material that asthma is twice as common in boys as in girls, but, on the contrary, is somewhat more frequently seen in girls than in boys after puberty. In Urbach's^{30,31} experience, figures covering the first two decades of life comprise more than twice as many boys as girls. Adam, Coke, Hansel, Peshkin, Salter, and others, in reports covering other allergies, have also shown that male incidence predominates in the first decade of life. From puberty to about the fiftieth year of life, allergic diseases are said to be found more frequently in women than in men, while from the fiftieth year on, men again seem to lead. In the ages from 15 to 45 years, according to Bray²⁹ and

TABLE 12—Estimated General Incidence of Allergy

Author	Year of Survey	Percentage
Spain W C, and Cooke R A	1924	7
Touton K	1925	7.10
Ratner B	1937	7.10
Bray G W	1934	10
Duke W W	1923	12.15
Service W C	1939	20
Rowe A H	1931	35
Jimenez B	1934	35
Pipes D	1937	50 { 14 major 36 minor
Vaughan W T	1934	60 { 10 major 50 minor

the Boston Recruiting and Induction Station in World War II, 4.95 (0.83 per cent) were disqualified for general military service because of severe allergic states (Hyde and Kingsley³²). In the examinations of 45,585 eighteen and nineteen year old registrants, asthma was detected in 5.3 and vasomotor rhinitis in 5.3 cases per thousand examined (Rowntree et al.³³). The respective rate for rejection for general military duty was 3.7 and 0.8. In addition, a certain proportion of the observed cases of sinusitis (1.2 per thousand) and of skin

²⁰ PINESS G and MILLER H. JAMA 80: 339 1925.

²¹ PIPES D M. South M J 30: 1012 1937.

²² SERVICE W C. JAMA 112: 2034 1935.

²³ M. Dept., U S Army in World War. Vol. 15. Statistics. Washington Govt. Printing Off. 1925.

²⁴ ROWNTREE L G, MCGILL K H and EDWARDS T I. JAMA 123: 181, 1943.

²⁶ BLANK P. J Lab & Clin Med 28: 629 1943.

²⁷ BLANK and LEVITT H. Ann Allergy 3: 113 1945.

²⁸ GOLD E M and BARKHOFF J M. J Allergy 15: 279 1944.

²⁹ URBACH E. Internat Clin 4: 89 1940.

Vaughan,²¹ allergic conditions are seen more often in females than in males, in a ratio of 5 to 4.

Somewhat different figures are reached, however, when one analyzes the distribution of the various allergic diseases according to sex but without considering age. The majority of authors (Adam, Coke, Hoffman, Piness, Rackemann) report a preponderance of males in respect to asthma, their totals ranging between 53 and 57 per cent. In 458 asthma cases, the senior writer^{23a} found 57.5 per cent male and 42.5 per cent female. For nasal allergy, on the other hand, Hansel^{23a} reported a higher incidence among women (54.3 per cent). The senior author^{23a} recently arrived at practically identical figures (54 per cent female, 46 per cent male). It is generally known that migraine is much more frequently observed in women than in men—the relative figures are 70 per cent as against 30 per cent. A similar

ably due to the fact that in Europe allergic diseases are not nearly as widespread as here, and that therefore the factor of heredity plays a considerably less important rôle abroad than here. Spain and Cooke^{23b} have shown that in asthma cases with bilateral inheritance of allergy, the symptoms become manifest during the first decade of life in 79.1 per cent of cases—as compared with figures of 36.3 per cent for those with unilateral inheritance, and of 21.7 per cent for those without inheritance. Similarly, Balyeat²³⁷ reported that if the inheritance is bilateral, allergic manifestations make their appearance before the age of 10 in 58.6 per cent of cases, in contrast to 32.3 per cent for this age if the inheritance is unilateral. These figures, do not, of course, take infantile dermatitis or strophulus into consideration.

With reference to *race incidence*, it may be said that, in principle, members of all races can become allergized. And this statement is in no way refuted by reports that hay fever and asthma are rarely observed, for example, among American and East Indians or native Japanese and Malaysians (Thommen), for, as we have already explained, allergy is unquestionably one of the dubious privileges of civilized peoples, and is thus a matter of social rather than of racial predisposition. It might pertinently be mentioned that, according to recent investigations, American Negroes are now showing a constantly increasing incidence of allergic diseases. In fact, asthma appears to be about 25 per cent more common in young Negro males than in whites (Rowntree et al.⁴¹⁹), although rhinopathy is comparatively much less common. The especially high incidence among the Jewish race may readily be explained by the fact that, especially in recent years in Europe, the Jews have been under great psychic strain, which constitutes an important predisposing factor in allergy. We have mentioned elsewhere Hara's interesting observation that the Japanese acquire hay fever in America but not in their native land (see p. 514). None of the existing evidence, in short, permits us to assume that there is such a thing as racial predisposition to allergy. The fact that the white race shows the highest incidence of allergy is obviously explained on

TABLE 13 — Sex Incidence of Urticaria

Author	Percentage		No. of cases
	Male	Female	
Fink and Gay	31	69	170
Stokes, Kulchar, and Pillsbury	33	66	100
Urbach	39	61	500

ratio is seen for urticaria, as is shown in Table 13.

According to Bray,⁷⁹ Rowe,²¹⁰ and others, the transmission of the allergic tendency seems to occur twice as frequently through the female as through the male; furthermore, twice as many offspring are likely to be affected in the transmission through the female.

With respect to *age distribution*, conditions in America and in Europe seem to differ. Numerous American authors (Rackemann, Hansel, Bray, and others) have frequently observed asthma, nasal allergy, and even migraine (Vaughan) in very young children. Only in recent years have the authors seen relatively numerous cases of hay fever in children 6 to 8 years old, while, despite a considerable material, asthma and rhinopathy were rather rare in this age group. All this is prob-

^{23a} HANSEL, F. K. Allergy of the Nose and Paranasal Sinuses. St. Louis: Mosby, 1936.

^{23b} URBACH, E. Arch. Otolaryng. 33: 582, 1941.

²³⁷ SPAIN, W. C., and COOKE, R. A. J. Immunol. 13, 93, 1927.

²³⁸ BALEYAT, R. M. Ann. J. M. Sc. 176: 332, 1925.

the basis of the higher plane of civilization with the peculiarly unfavorable influences involved.

It has often been pointed out that blond blue eyed, fair skinned persons not only have more sensitive skins than dark haired dark eyed persons but are also more readily allergized. It is noteworthy in this connection that most eczematous infants and children have blue eyes and light hair. On the basis of epidermal allergization experiments Rostenberg and Kanof³⁵⁵ report that Negroes are less readily sensitized than are white persons. This is confirmed by actual experience in industry (L. Schwartz). The investigator explains this on the basis of their relatively greater sebaceous secretion which may act as buffers or neutralizers of the sensitizing substances. These remarks apply, of course, only to allergic skin diseases.

Finally mention must also be made of Coca's interesting observation that the incidence of asthma, hay fever and other allergic diseases in the insane is less than 0.1 per cent—as compared with a figure of 3.5 per cent for the population as a whole. In fact among the 3,700 patients of the Rockland (N. Y.) State Hospital for the Insane, Blaisdell has seen only 2 cases of hay fever and 1 case of asthma.

And Roger Reid of the Department of Mental Hygiene of the State of New York found among the 2,900 mentally deficient inmates of Letchworth Village (N. Y.) only 2 cases of asthma. MacInnis³⁵⁹ not only confirmed the strikingly low incidence (0.07 per cent) of allergic symptoms in 7,000 psychiatric patients but actually observed 3 cases in which allergic manifestations improved or disappeared during mental illness and recurred on an approach of mental balance. Levitt³⁶⁰ likewise found only ten cases of asthma among 11,647 patients with functional psychosis, an incidence approximately one twentieth normal and not a single case among more than 5,000 institutionalized epileptics and mental defectives. No adequate explanation of these findings has been offered.

Zeller and Edlin³⁶¹ point out however that this apparent infrequency of allergy in psychotics is probably due to their failure to voice their complaints and to the lack of frequent general physical examinations. They observed the same incidence of hay fever and asthma as in the sane and also concluded that the degree of mental imbalance does not influence the severity of hay fever.

³⁵⁵ ROSTENBERG, A. JR. and KANOF, N. M. J. Invest. Dermat. 4: 505, 1941.

³⁵⁹ MACINNIS, K. B. J. Allergy 8: 73, 1937.

³⁶⁰ LEVITT, H. C. Psychosom. Med. 5: 39, 1943.

³⁶¹ ZELLER, M. and EDLIN, J. V. J. Allergy 14: 364, 1943.

CHAPTER VI

THE EXPERIMENTAL BASIS OF ALLERGY

A CONSIDERABLE part of the material pertaining to this subject has already been discussed elsewhere (see experimental allergization of animals, p. 42). Those investigations that deal with the experimental production of allergies in particular organs, such as the blood vessels, intestines, etc., will be considered in the relevant chapters of Part Three. We shall limit ourselves here mainly to a discussion of experimental anaphylaxis, as defined on page 8. And we wish to stress once again that this represents a special form of allergy, and is by no means to be regarded as the fundamental type. However, since the experiments on anaphylaxis have aided in establishing a number of important laws of allergy, it is essential to review them in some detail.

A. EXPERIMENTAL ANAPHYLAXIS

There is a distinction between active and passive anaphylaxis, depending on whether the antibodies are actively produced by the tissues as a result of contact, or are passively administered to the organism. A differentiation is also to be made between general and local anaphylaxis—the latter being the basis of the Arthus phenomenon. A special type of passive anaphylaxis is represented by “inverse anaphylaxis,” in which the procedure reverses the usual order of administration, the antigen being injected first and then the antibodies.

1. GENERAL ANAPHYLAXIS

The following three conditions must be fulfilled to achieve *active* anaphylaxis: (1) the preparatory or anaphylactizing contact; (2) an appropriate period of latency, called, by analogy, the “incubation period,” during which the organism produces antibodies, and (3) the subsequent, eliciting contact.

The difference between experimental anaphylaxis in animals and allergy in human beings consists only in the fact that, in the latter, the allergization does not generally take place following a single massive contact, but rather as the result of numerous, frequently repeated,

quantitatively smaller exposures to the antigen, furthermore, the manner of exposure in the case of human beings is usually by way of the digestive or respiratory tract, or the skin, and differs therefore from that in animal experiments. Recent investigations have shown, however, that lethal anaphylaxis in animals can also be achieved when the preparatory and/or the eliciting contact with the anaphylactogen occurs otherwise than by injection. This constitutes further evidence in support of the concept that the difference between anaphylaxis and allergy is entirely quantitative and not qualitative.

The term *anaphylactogen* is used for the antigens with which experimental anaphylaxis can be produced. Not every antigen is suitable for this purpose: animal protein possesses the best anaphylactogenic properties. The factors having the greatest influence on the induction of anaphylaxis are: (1) the species of animal involved, (2) its race, (3) its age, (4) the diet, (5) the endocrine function, and (6) the temperature.

Thus, animal species vary greatly with respect to the ease with which they may be rendered anaphylactic. Guinea pigs can be anaphylactized with minute amounts of antigen, whereas rabbits and dogs require larger multiple doses and even with these may show only mild symptoms of shock. Not all the members of a given animal species are alike in their susceptibility to anaphylaxis. Thus, of the subspecies of guinea pigs, according to B. C. Seegal, only the Brazilian breed are refractory. Thomsen and other authors found that both very young and very old guinea pigs are extremely difficult to anaphylactize. Sartori, Sereni, and others claim that animals are more readily rendered anaphylactic on a diet deficient in greens (see also p. 67). Seegal and Khorazo state that rats on a complete diet cannot become anaphylactic, but can if maintained on a diet of white bread and water. Flashman and Wyman found that adrenalectomized white rats could readily be allergized and thrown into shock. Thyroidectomy, on

the other hand renders guinea pigs incapable of active anaphylactization although they can be passively allergized (Kepinow and Lanzenberg, Fleischer and Wilhelm). Aside from these constitutional endocrine age and dietary influences physical factors can also influence sensitivity. Thus Friedberger and Seidenberg report that guinea pigs kept at a temperature of 6 C. will fail to become anaphylactized to sheep serum whereas control animals kept at temperatures of from 17 to 21 C. become highly allergic to this antigen. At the other extreme of temperature Gottschall et

The first anaphylactic manifestation in the guinea pig consist of severe itching as evidenced by scratching of the muzzle ears and paws. The coat is then seen to bristle leading to the appearance of the so called lion's head (Figs 16-17). Furthermore there is a strange sort of gagging and retching accompanied by coughing which in turn is followed by severe dyspnea (Figs 18-19) this finally brings on death by suffocation within a few minutes. Immediately preceding death there is a discharge of feces urine and seminal fluid. These symptoms may all be explained as due



FIG 16

FIG 17



FIG 18

FIG 19

ANAPHYLACTIC SHOCK IN GUINEA PIGS

FIG 16 Normal appearance

FIG 17 Slight shock lion's mane (bristling of coat)

FIG 18 Normal appearance

FIG 19 Severe shock dyspneic reaction comparable to human asthma

al³⁶ found that artificially induced fever of sufficient degree and duration will protect previously sensitized guinea pigs against anaphylactic shock. For some reason older guinea pigs were much more readily protected than young ones.

The clinical manifestations of anaphylaxis depend entirely upon the species of the animal used. On the other hand the greatest variety of anaphylactogens will elicit the same clinical picture in all animals of a given species.

to spastic contraction of the smooth musculature. The bronchial stenosis is so extreme that the lungs do not collapse when the thorax is opened.

In rabbits the smooth muscle spasm occurs in the pulmonary vessels. This creates such resistance to the flow of blood from the right ventricle that the heart fails and the animal dies of circulatory asphyxia.

In dogs the smooth muscle spasm occurs in the hepatic veins (E. P. Pick) which in this species possess unusually large amounts of smooth muscle tissue. This leads to hepatic

³⁶ GOTTSCHALL, R. J., DE KROM, P., COPE, H. E. and LAURENT, D. J. Lab & Clin Med 29: 614, 1944.

stasis, with consequent engorgement of the splanchnic vessels and a very pronounced drop in blood pressure, increased capillary permeability, severe and often bloody diarrhea, dyspnea, and general muscular weakness. Blood coagulability is lost and the leucocytes disappear from the peripheral vessels. Very few animals survive these acute manifestations.

Rats respond with symptoms similar to those shown by dogs (Crocker and Parker).

In *cats*, it seems likely that smooth-muscle spasm in the intestines is the cause of increased intra-intestinal pressure and fall in blood pressure and in temperature. At the same time, the kidney volume is decreased, probably owing to spasm in the renal arteries.

In *pigeons* the reaction occurs in the smooth muscles of the crop (Hanzlick).

In *rhesus monkeys* there is salivation, vomiting, bleeding from the anus, prostration, cyanosis, decrease of the blood platelets, and loss of consciousness. In experiments in which fatal shock was delayed for twenty-four hours, edema of the face was noted (Kopeloff and Kopeloff). Local skin testing is followed by reactions of the character of the Arthus phenomenon (edema, necrosis, hemorrhage).

In *horses* and *cattle*, the anaphylactic response is chiefly intestinal, with diarrhea as the outstanding symptom.

The various responses in the different animal species can be partly explained on the basis of anatomic differences. Thus, in the guinea pig the musculature of the bronchioles is particularly well developed, whereas in rabbits a similar condition is found in the musculature of the pulmonary artery, and in dogs in the hepatic vessels.

In contrast to animals—where all members of a given species respond with the same clinical manifestations—*human beings* possess a number of shock organs, of which only one or a combination may be involved. This explains why anaphylaxis in human beings may evoke a variety of clinical pictures—asthma, angioneurotic edema, intolerable itching, depressed blood pressure, diarrhea, intestinal hemorrhage, hepatic stasis, convulsions, dizziness, etc. (For further details, see p. 484.)

A review of the various manifestations of shock in animals and in human beings makes it clear that all these symptoms are attributable

to an antigen-antibody reaction, in the smooth muscle, in the mucous membranes, or in the capillary endothelium.

While the majority of investigators hold that the unstriated muscle fibers are the fundamental shock structure in some organs, Albert and Walzer³⁰³ dispute this concept, because they were unable to elicit specific contractions of the intestine in sensitized monkeys with the Schultz-Dale technic.

The smooth-muscle reaction takes the form of spasm. This can be observed *directly* (bristling of the animal's coat, contractions in the gastro-intestinal tract demonstrable by X ray), or *indirectly* (gastro-intestinal spasm as evidenced by colic, fecal, urinary, and seminal incontinence), or the spasm may be demonstrated in isolated organs by means of the Schultz-Dale technic.³⁰⁴ This last-named method in particular has confirmed the importance of the smooth musculature of the bronchi, stomach, intestines, gallbladder, urinary bladder, uterus, and blood vessels as shock tissues. Since this is one of the most accurate and efficient methods of demonstrating the anaphylactic state, we shall briefly describe the Schultz-Dale test.

Technic The isolated viable uterine horns of allergized virgin guinea pigs are suspended in warm oxygenated Ringer's solution. Addition of the specific antigen is followed by an antigen-antibody reaction which produces a contraction of the musculature, registered as a sharp rise of a recording stylus. As evidence of the specificity of this reaction, the uterine musculature proves to be "deallergized" thereafter—i.e., no longer reacts, although it is still fully capable of being stimulated by addition of pituitrin or histamine. The deallergization is due to the fact that the first administration of antigen has neutralized all the antibodies (Fig. 20). Hartley's recent investigations have shown that uteri of normal guinea pigs can be passively sensitized by the addition of antiserum to the Ringer's solution, provided the antiserum is of adequate potency.

Second to the smooth musculature in order of importance, we should probably rank the *capillary endothelium*, in regard to its significance as the site of anaphylactic reactions. According to Doerr¹³ the capillary and pre-capillary vessels react to the anaphylactogen with changes in caliber (dilatation and constriction) and with changes in permeability, leading to

³⁰³ ALBERT, M. M., and WALTZ, M. J. *Immunol.* 44: 263, 1942.

³⁰⁴ DALE, H. H. *J. Pharmacol. & Exper. Therap.* 4: 167, 1913.

edema and diapedesis. It is possible to observe microscopically the reactions of the capillaries by severe circulatory disturbances consisting chiefly of a fall in the systolic blood pressure.

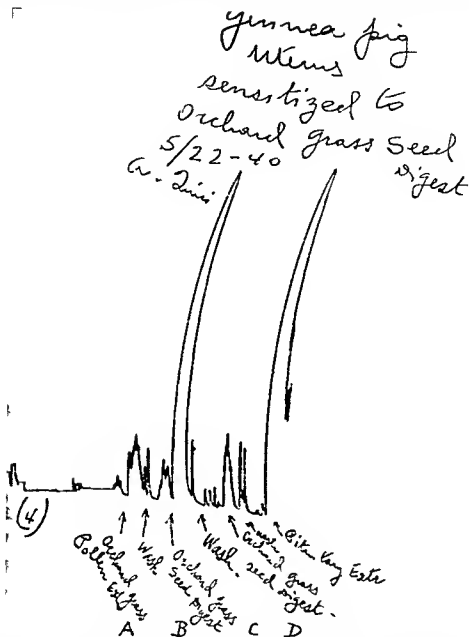


FIG. 20 SCHULTZ DALE TEST

Employing isolated horn of virgin guinea pig allergized six weeks before with orchard grass seed digest. There is no reaction to orchard grass pollen (A) but maximal contraction in response to orchard grass seed digest (B). Second addition of seed digest produces no reaction as evidence of deallergization (C) while pituitary extract is again followed by maximal contraction (D).

laries when serum is dropped on the exposed mesentery of a specifically allergized frog. Clinically, the capillary response is manifested

probably due to dilatation of the blood vessels in the splanchnic area in the liver, and elsewhere. Furthermore, there is a rather mild

generalized capillary hyperpermeability, which is observed not only in human beings but also in numerous species of animals

The effect of these pathologic changes can be demonstrated in the isolated organ of the sensitized animal by means of the lung perfusion test or Manwaring-Kusama technic.³⁶⁵

Technic The animal is killed and the lungs and heart exposed. The perfusion fluid consists of Lockes' solution to which is added the appropriate antigenic material. It is introduced into the circulatory system of the lung by means of a cannula in the pulmonary artery, and after passing through the lungs, allowed to escape through a puncture in the left auncle. Both the perfusion solution and the lung tissue are maintained at a temperature of 40 to 42 C by means of a suitable heating arrangement. During the perfusion, the lungs are alternately inflated and allowed to collapse by means of air forced in through a tracheal cannula, in a manner simulating the normal respiratory movements.

Note is made of the resulting changes in resistance to inflation, and in the promptness and completeness of expiratory collapse. A positive lung perfusion test is shown by the increased size of the lung due to the entrapped air (Fig. 23). A negative or unsensitized or deallergized lung (Fig. 24) shows no increase in size when compared with a normal control lung.

Finally, the liver was at one time assigned an important rôle in the pathogenesis of anaphylaxis. This, however, has been proved only for experimental shock in dogs and probably rats. The classic experiments of Manwaring showed that hepatectomized dogs could not be thrown into anaphylactic shock. Pick explains this on the basis of the assumption that the smooth musculature of the hepatic veins is the chief shock tissue in this animal. In disagreement with other authors, Doerr holds that the shock tissue in dogs is the capillary endothelium and not the musculature of the blood vessels of the liver. Others have entertained rather vague theories holding that the liver parenchyma itself is the site of the antigen-antibody reaction. More recent investigations by Dragstedt³⁶⁶ and others suggest the possibility that a vaso-active histamine-like substance is liberated into the blood stream by the liver during anaphylactic shock. Winter^{366a} found that injection of the shocking dose of antigen by way of the portal vein was more effective in producing gross anaphylaxis in

guinea pigs than was injection into the systemic circulation, indicating that cells in the liver of this species are sensitized and that an antigen-antibody reaction in this organ contributes to the anaphylaxis. While these theories explain the fall in blood pressure during shock, they do not account for the decreased coagulability of the blood. The latter was shown by Jacques and Waters³⁶⁷ to be due to the presence of heparin in the blood stream, presumably liberated from the liver.

It is now accepted as an established fact that anaphylactic manifestations are the result of an antigen-antibody reaction. This is indicated above all by the fact that it is possible to transfer anaphylaxis passively by means of blood serum from anaphylactic individuals, as well as to achieve specific hyposensitization.

The following experiments all indicate that the antigen-antibody reaction takes place in the tissue cells and not in the circulating blood. When the blood of an allergized animal is totally replaced by normal blood, administration of the antigen will nevertheless elicit the anaphylactic phenomenon characteristic of the given animal species (Fenyvessy and Freund). When an animal receives an injection of antibody-containing immune serum, and when 98.5 per cent of its blood is then replaced by transfusion of blood from a normal animal, adequate exposure to the antigen will be followed by a characteristic anaphylactic reaction (Doerr). Another convincing experiment was performed by Kritchewski and Friede. They allergized frogs by injecting rabbit serum into the lymphatic sac. Several days later they withdrew the blood and thoroughly washed the vascular system with Ringer's solution. Shortly after, the injection of a small amount of rabbit serum into the abdominal vein elicited typical anaphylactic shock. But the clearest and most unequivocal proof of the cellular nature of anaphylaxis is to be found in the reactive capacity of surviving isolated bloodless organs, as is demonstrated in the Schultz-Dale experiment on the uterus and small intestine, and in the lung perfusion experiment of Manwaring and Kusama.

There is as yet a considerable diversity of opinion as to just how the antigen-antibody

³⁶⁵ MANWARING, W., and KUSAMA, G. *J. Immunol.* 2, 157, 1917.

³⁶⁶ DRAGSTEDT, C. A., and MEAD, F. B. *J. Immunol.* 39, 319, 1936.

^{366a} WINTER, L. B. *J. Physiol.* 104:11, 1945.

³⁶⁷ JACQUES, L. B., and WATERS, E. T.: *Am. J. Physiol.* 129, 359, 1945.

reaction brings on anaphylactic shock. We have elsewhere (p. 36) discussed in some detail the two most important theories—the physical and the chemical. We shall now merely call attention to the interesting fact that the shock can be temporarily eliminated or at least weakened by a great variety of physical measures (surgery, performance of muscular exercises, exposure to a temperature of $+1^{\circ}\text{C}$, or induced hyperpyrexia) or chemicals (dextrose, barium, lipid solution, sodium thiosulfate, narcotic drugs, blockade of the reticulo endothelial system with India ink or colloid dyes). This would surely tend to indicate the physical origin of the shock mechanism. It must be emphatically stressed, however, that these measures may prevent the occurrence of the shock, but not the underlying antigen antibody reaction. This is demonstrated by the fact that after the influence of the physical and chemical agents has subsided, shock may readily be elicited again.

Besredka assumed that narcotics exert their anaphylaxis inhibiting influence by way of the central nervous system. Davidoff and his co-workers showed, however, that sensitized monkeys reacted with typical shock even when decerebrated before the eliciting dose. Farmer is of the opinion that urethane, ether and other drugs act either directly on the musculature or inhibit shock by virtue of their relaxing effect—in other words, they influence the peripheral organs.

2 LOCAL ANAPHYLAXIS

In contrast with general anaphylaxis, *local* anaphylaxis designates pathologic changes in circumscribed areas of the tissues—as seen at the site of administration of the antigen in allergized individuals. Two phenomena should be considered here. The first is the local reaction that results when a specific antigen is injected directly into the tissues of a systemically sensitive animal. This type of reaction is represented by the positive immediate and delayed skin reactions to the various food proteins, epidermal substances, and other antigens, and also by such clinical symptoms as those of the gastro intestinal tract after the ingestion of certain foods. Seegal, Seegal, and Jost succeeded in eliciting local reactions in the pericardium, aorta, and brain of allergized

rabbits by means of local injections of the homologous antigen.

The second phenomenon was described by Arthus and bears his name. The *Arthus phenomenon* designates the vehement local reactions (Fig. 21) sometimes leading to actual necrosis, following repeated and usually massive injections of foreign serums. It is not necessary to inject into the same site in order to evoke the characteristic response. Thus, for example, the early injections might be made



FIG. 21 ARTHUS PHENOMENON (LOCAL ANAPHYLAXIS)

Erythema, swelling and brawny infiltration at site of injection of prophylactic tetanus antitoxin (prepared from horse serum) in patient who had received antitetanus injection some weeks before because of another injury.

into the peritoneum, the subsequent ones into the skin. The tissue necrosis in the Arthus reaction results primarily from impairment of nutrition, due to vascular damage and to clogging of the tissue spaces with exudate and hemorrhage (Rich and Tollis). The histologic picture of the Arthus phenomenon is characterized by extensive infiltration of the skin and subcutaneous tissue with polymorphonuclear, mononuclear, and eosinophilic leucocytes and by marked edema throughout the connective tissue fibers, followed by a degeneration of this

tissue to a homogeneous mass, with hemorrhages even in the deeper layers. It should be especially noted that eosinophile cells are locally demonstrable early in the reaction.

It is interesting to consider that evidences of general hypersensitiveness are also observed in so-called local anaphylaxis. Thus, Grégoire points out that, in addition to the edema and the hyperplasia of the germ centers and reticulo-endothelial cells of the regional lymph nodes in allergized animals, there is also a reaction of the other lymph nodes of the body—of course in a lesser degree. Cannon and Marshall³⁶³ report that the intensity of the inflammation in the Arthus phenomenon is parallel to the variations in the precipitin titer of the serums of animals injected with crystalline egg albumin. They also observed a constant correlation between the antibody content of serum and its ability passively to induce the Arthus phenomenon in the rabbit.

Local anaphylaxis of the necrotic type is not frequently seen in clinical medicine. As an example we may cite Ross's³⁶⁹ interesting case. A boy 4 years of age, who had received a toxin-antitoxin injection a year previously for immunization against diphtheria, suffered an injury and was given a prophylactic injection of tetanus antitoxin. Three days later the child presented an exanthem resembling scarlet fever, along with fever and sore throat. Streptococcus antitoxin was administered intragluteally. Shortly after, local reddening and infiltration appeared, followed within a few days by necrosis, which led to death.

However, the fact is certainly striking that despite innumerable prophylactic and therapeutic injections of serum that have been given—and in large doses, particularly years ago—there have been very few instances of local manifestations corresponding to the experimental Arthus phenomenon. Search of the literature revealed only the following reports: Lucas and Gay,³⁷⁰ Péhu and Durand,³⁷¹ Hegler,³⁷² Koehler and Heilmann,³⁷³ Gatewood and

Baldrige,³⁷⁴ Meleney,³⁷⁵ Tumpeer,³⁷⁶ Irish,³⁷⁷ Marooney,³⁷⁸ Kohn, McCabe and Brem,³⁷⁹ Brown, Griffiths, Erwin, and Dyrenforth,³⁸⁰ Gougerot and Blum,³⁸¹ and Greenbaum.³⁸² In all of the cases of these reports except 2, severe local necrotic reactions appeared at the site of repeated injections of toxin-antitoxin administered in the course of an acute infectious disease, such as scarlet fever, diphtheria, or meningitis. In Brown's³⁸⁰ case the reactions were due to mosquito bites, and in Greenbaum's to repeated injections of histaminase. As mentioned above (p. 33), Schwartzman,¹⁴⁸ Harkavy and Romanoff,³⁴⁹ and others denied that these were anaphylactic reactions, i.e., instances of the Arthus phenomenon; on the contrary, they considered these necrotic processes as expressions of nonspecific local tissue reactivity (Schwartzman phenomenon).

Opinions differ about the mechanism of the Arthus phenomenon, mainly as regards the relative importance of humoral and cellular antibodies in its development, the influence of variations of antibody concentrations upon the intensity of the inflammatory reaction, and the relationship of the latter to resistance in general. Cannon and Marshall³⁶³ found that (1) in every instance in which the Arthus phenomenon was produced, specific precipitins were likewise demonstrable in the serum at the time of the cutaneous test and, (2) there is a definite parallelism between the precipitative potency of the serum and the intensity of cutaneous reactivity. The Arthus phenomenon is dependent upon the union within the tissues of circulating precipitin and its specific antigen.

3. PASSIVE ANAPHYLAXIS

Experimental anaphylaxis can be achieved not only actively, but also passively, using antibody-containing blood. The experiments of Kabat and Landow³⁸³ reveal how small a

quantity of antibody is necessary to produce passive allergization. The intravenous injection of 0.03 mg of rabbit antibody nitrogen will passively sensitize a guinea pig so that fatal anaphylaxis will result on the injection of 1 mg of egg albumen or 0.1 mg of type III pneumococcus polysaccharide. The isolated uterus need contain only 0.01 microgram of antibody for contraction to be elicitable.

Until recently it was accepted as axiomatic that a latent or incubation period of at least four hours was essential for the induction of anaphylaxis. We now know that rabbits and mice react immediately not only to the introduction of antibody and antigen in rapid succession but also to the injection of a mixture of both. We have discussed elsewhere the few cases of passive anaphylaxis that have been observed in clinical medicine. Here we shall consider mainly *reverse* or *inverse passive* anaphylaxis which promises to be of theoretic and also of considerable practical significance. The term designates the following procedure: the antigen is first administered locally and some time later the antibody containing serum is injected intravenously intraperitoneally or otherwise bringing on typical symptoms of anaphylactic shock. (Opie and Furth³⁴⁴ Kellett³⁴⁵) Lehner and Rajka reported the reverse passive transfer of anaphylactic response to mustard oil. They caused 2 guinea pigs to inhale mustard oil twenty four hours later the intraperitoneal injection of human serum from a patient allergic to this substance resulted in the death of the animals with the characteristic pathology of anaphylaxis. Zinsser and Enders³⁴⁶ obtained positive results even when the interval between the injections of antigen and of serum was only one and a half minutes. Nevertheless these authors do not consider that these findings negate the theory of a cellular site of the anaphylactic reaction as might be assumed from the surprisingly short time needed for the specific response.

Swineford³⁴⁷ produced reversed passive anaphylaxis in guinea pigs and rabbits by means of intra abdominal and intravenous injections of pneumococcal polysaccharides followed at

varying intervals by the intravenous injection of specific antipneumococcal rabbit serum. On this basis as well as the clinical evidence he suggests that anaphylactic reactions following administration of immune serum in human patients with pneumonia may be due to the same phenomenon—the antigen being supplied by the infecting organism in vivo and the anaphylactic antibody by the injected serum.

Voss³⁴⁸ employed the principle of inverse passive anaphylaxis to achieve deliberate local manifestations of serum sickness with the object of preventing general serum sickness. He injected 1 to 10 cc of convalescent serum from a case of serum sickness intravenously in children at various intervals after the therapeutic administration of diphtheria antitoxin. When this was done within the first three days after the antitoxin was given a wheal and erythema appeared at the site of the antitoxin injection when it was done after the fourth day the rash was generalized and when injection of the convalescent serum was delayed until the eighth or ninth day (i.e. the very end of the incubation period of serum sickness) the symptoms approached shocklike intensity. Spontaneous serum sickness was prevented in these children by this procedure (see p. 354).

When normal children were injected with horse serum intracutaneously and then about eight hours later received convalescent serum injected intravenously, they showed clear cut reactions at the site of the first injection. Extremely high dilutions (1:100,000) of the horse serum gave reactions that were almost as strong as those to the undiluted serum. This method affords an opportunity for demonstrating the presence of anaphylactic antibodies. Karelitz and Glorig³⁴⁹ generally confirmed Voss' work but also demonstrated species specificity in that serums from other animals did not react with serum sickness convalescent serum specific for horse serum. The antibodies were thermostable and their presence could also be shown by the Prausnitz-Kuestner method by either the usual or the reverse technique. Szirmai's³⁴⁹ experimental work likewise corroborated the findings of Voss.

³⁴⁴ Opie E. L. and Furth J. J. *Exper. Med.* 43: 469, 1926.

³⁴⁵ Kellett C. E. *J. Path. & Bact.* 41: 479, 1935.

³⁴⁶ Zinsser H. and Enders J. F. *J. Immunol.* 50: 327, 1936.

³⁴⁷ Swineford O. Jr. *J. Allergy* 16: 221, 1945.

³⁴⁸ Voss E. A. and Huxford O. *Ztschr. f. Immun. taetsforsch. u. exp. The.* 49: 281, 1933.

³⁴⁹ Karelitz S. and Glorig A. *J. Immunol.* 47: 121, 1943.

³⁵⁰ Szirmai F. *Arch. f. Knoch.* 117: 56, 1939.

For an extensive critical review of the literature on anaphylaxis, the reader is referred to Dragstedt.³²¹

B. EXPERIMENTAL BASIS OF SPECIFIC HYPOSENSITIZATION (DESENSITIZATION)

As is well known, the term *hyposensitization* (*desensitization*) designates the procedures in which the organism is given small quantities of antigen in repeated and increasing doses, with the result that the blood then contains an excess of free circulating antibodies. This concept is based on the results of the following experiments. When allergized animals are treated with increasing amounts of antigen injected at intervals of several days, subsequent administration of a usually lethal dose will be tolerated without manifest symptoms, although the lungs (in the perfusion experiment) and the uterus (in the Schultz-Dale experiment) are still anaphylactic—in other words, have a high antibody content. At the same time, it is always possible to perform passive transfer with blood serum from the *hyposensitized* animals. It is commonly accepted, therefore, that the refractoriness of *hyposensitized* animals may be explained on the basis of an excess of *free circulating antibodies*. These conditions are summarized in the third line of Table 14 (p. 93).

So long as there is an excess of free antibodies in the blood, the individual does not give manifest responses to renewed administration of antigen; this may be explained on the grounds that the antigen is so completely neutralized in the blood that it cannot enter into an antigen-antibody reaction with the sessile antibodies in the tissues. This working hypothesis (Weil³²²) serves to explain how, at a time of complete clinical insensitiveness, there can be positive skin reactions to local (e.g., intradermal) administration of the allergen, and, above all, the fact that shortly after the administration of the antigen is stopped, the organism again appears clinically to be strongly hypersensitive. The reason is that in the absence of further antigen administration, production of excess circulating antibodies ceases, so that antigen later administered will react directly

with the cellular antibodies, thus causing allergic manifestations.

A considerable mass of evidence contradicting this hypothesis of the mechanism of hyposensitization in animal anaphylaxis (but not the Arthus phenomenon) and in human allergies has accumulated in recent years, and is summarized by Sammis¹¹⁵ and Bronfenbrenner¹¹⁹. Thus, Morris³²³ showed that administration of additional antibody to passively sensitized guinea pigs did not increase refractoriness to anaphylaxis, but actually enhanced the sensitivity. Hence he concluded that an excess of circulating antibody is not responsible for a state of antianaphylaxis. Moreover, the refractory state in hyposensitization may be reached long before any increase in circulating antibodies could possibly be attained. The alternative concept that hyposensitization is established by saturation or neutralization of the cellular or sessile antibody is discarded by Bronfenbrenner on the grounds that in animals possessing an excess of circulating antibody, such a state would be impossible or difficult to attain. Likewise, a determination of antibody content of the serum of sensitized, as well as desensitized, guinea pigs indicates that the loss of reactivity in the latter cannot be adequately accounted for on the basis of depletion of antibody. Moreover, the resensitization of desensitized animals revealed that they could tolerate many times the amount of antigen as compared with passively sensitized animals. A further argument is found in the fact that when animals simultaneously sensitized to two or more antigens are given a "desensitizing" injection of one of them, they become more or less refractory to all other antigens at the same time. Morris concludes that antianaphylaxis is the result of secondary non-specific changes, the true nature of which is not definitely established.

Bronfenbrenner¹¹⁹ holds that anaphylaxis results from the activation of serum trypsinase through the physico-chemical changes initiated by the antigen-antibody union. Antianaphylaxis, then, is mediated by an antitryptic effect of the products of the digestive activity of the trypsinase. This was confirmed in part by Burden.³²⁴ The antitryptic effect is identi-

³²¹ DRAGSTEDT, C. A. • Physiol. Rev. 21: 546, 1941.

³²² WEIL, R. J. Med. Research 27: 492, 1913.

³²³ MORRIS, M. C. J. Exper. Med. 64: 641, 657, 1936.

³²⁴ BURDEN, K. L. Proc. Soc. Exper. Biol. & Med. 49: 24, 1942.

fied with the polypeptides, but other substances, such as serum albumin, unsaturated fatty acids, and heparin have a similar action. Non specific "anaphylactoid" agents owe their antianaphylactic effects to a similar mechanism in elevating the antitryptic titer. This concept is shown diagrammatically in Fig 22.

There is suggestive evidence that the blocking or thermostable antibody (p 142) may be responsible for hyposensitization in human beings.

Correctly evaluating the mechanism (temporary clinical insensitiveness, without cure), Cooke and also Levine and Coca are opposed to the designation "desensitization." They prefer the term *hyposensitization*, in recognition of the fact that this method has not solved the

that in the course of hyposensitization treatment there are certain phases during which—temporarily at least—the antibodies are totally neutralized. This is shown by the lack of reaction of the isolated uterus and lungs. Such phases are observed when a large deposit of antigen is being gradually absorbed by the organism. Further investigative studies will be necessary to determine just which hyposensitization methods can lead to permanent deallergization.

If the antigen is not known or is an endogenous allergen, *heterospecific hyposensitization* may be attempted. This is based on systematic administration of minute, slowly increasing doses of hetero allergens such as tuberculin, peptone, and similar substances, producing a

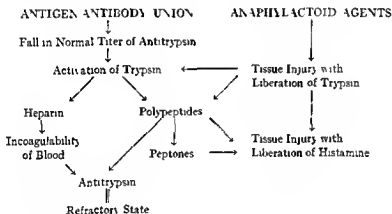


FIG 22 DIAGRAM OF MECHANISM OF ANAPHYLAXIS AND REFRACTORY STATE (ACCORDING TO BROFENBRENNER¹¹³)

fundamental problem—namely, prevention of further antibody production upon which the continuance of the allergic state depends. Under certain conditions, however, hyposensitizing measures may lead to deallergization (see below), as demonstrated by Dale¹⁶⁴ in animal experiments and confirmed in clinical practice. Sherman and Stull¹⁶⁵ achieved lasting insensitiveness in hay fever patients by means of very long courses of hyposensitization measures, creating a permanently raised threshold of tolerance to the antigen. But, in principle, the clinical results achieved with hyposensitization therapy still depend on regular administration of the antigen.

Our own investigations have convinced us

marked increase in the *specific* antibodies in the blood. The supposed antigen is thus prevented from entering into a reaction with the cellular antibodies which, in turn, prevents the occurrence of allergic manifestations. The experimental basis of this concept has been discussed in detail in the section on hetero allergy (p 24).

C EXPERIMENTAL BASIS OF DEALLERGIZATION

The term deallergization, introduced by the senior author,¹³⁴ designates all the therapeutic measures by which antibodies actively produced by the organism are counteracted through the appropriate administration of

* SHERMAN W B and STULL A. J Allergy 10: 455 1939

¹¹³ BROFENBRENNER E. J Invest Dermat 3: 493 1940

antigen; the antibodies are thus neutralized or otherwise rendered incapable of reacting. This results first in the consumption of the tissue antibodies and later in the arrest of production of specific antibodies. In this manner, the entire organism—or the principal shock tissues—are rendered insensitive, permanently or for a certain length of time. Accordingly, we may differentiate between a total and a partial, and between a permanent and a temporary deallergization. The three following combinations may result, and can be demonstrated by animal experiments: (1) the partial-temporary, (2) the total temporary, (3) the total-permanent state of deallergization.

It must be especially emphasized that deallergization methods, at least at present, can be

—that is, when the dose brings on a severe anaphylactic shock that, however, does not cause immediate death, but is followed either by death after one to two hours, or by ultimate survival of the animal after the most severe and long-lasting manifestations. As demonstrated (Urbach²⁹⁶) by the lung perfusion experiment, as well as by the Schultz-Dale test, the organs of an animal thus exposed to long-lasting shock become deallergized for the duration of its life—in other words, no antigen-antibody reaction occurs. If, on the other hand, the reinjection brings on *acute*, lethal anaphylactic shock, the lungs and uterus of the animal are found to be still highly sensitive.

The results of these two experiments conform perfectly with the theoretic expectations. For,

TABLE 14—Summary of Mechanisms of Anti-allergic Methods (Urbach²⁹⁶)

State of Animal	Type of Protection	Effect of Shock Dose	Perfusion of Isolated Lung	Dale Test on Uterus	Passive Transfer
Nonallergized	—	—	—	—	—
Allergized	none	+	+	+	+
Allergized	hyposensitization by increasing doses of antigen at intervals of more than 2 days	—	+	+	+
Allergized	deallergization by massive doses of specific antigen, causing severe macroshocks	—	—	—	—
Allergized	deallergization by injection of specific antigen, causing slight macroshocks, freedom from symptoms on subsequent massive doses of antigen	—	—	—	—
Allergized	deallergization by preceding doses of intravenous specific antigen (skeptophylaxis), orally acting through microshocks	—	—	+	+
		—	—	—	—

applied only with nonliving antigenic material. In animal experiments, specific deallergization can be achieved (1) by massive doses of specific antigen, causing severe macroshocks, (2) by injections of specific antigen, causing slight macroshocks, with a symptom-free state on subsequent massive doses of antigen, and (3) by means of specific skeptophylactic methods acting through microshocks, (a) intravenously or (b) orally (see Table 14).

1. DEALLERGIZATION BY MASSIVE DOSES OF SPECIFIC ANTIGENS CAUSING SEVERE MACROSHOCKS

Deallergization by means of overloading with antigens succeeds only when the proper dose of antigen has been chosen for reinjection

in the case of lethal shock, there is insufficient time for the tissue antibodies to be neutralized by the administered antigen, while, in case of survival, the slow neutralization brings about total and permanent specific insensitiveness of the lungs and uterus.

2. DEALLERGIZATION BY INJECTIONS OF SPECIFIC ANTIGEN LEADING TO SLIGHT MACROSHOCKS

In the course of anti-allergic treatment (Besredka²⁹⁷), it is possible, either accidentally or intentionally, that the first or one of the later injections may cause clinical anaphylactic manifestations, even though slight. In such

²⁹⁷ BESREDKA, A. *Théorie de l'anaphylaxie*. Paris, Masson, 1927.

a case the animal will be completely refractory to a reinjection with a multiple of the lethal dose—provided the reinjection is not given until after four hours have elapsed. The basic mechanism here is different however from that which results in protection from skeptophylactic injections. For reinjection with a lethal dose (after four hours) in animals that have survived such slight macroshocks shows these animals to be totally deallergized—i.e. no antibodies can be found in the lungs or uterus nor can the hypersensitiveness be transferred. In guinea pigs treated skeptophylactically by intravenous injection on the other hand the uterus contains abundant antibodies (positive Schultz Dale test) and the hypersensitiveness can be transferred passively by way of the blood serum. Moreover prior to this reinjection there is only a partial deallergization of the lungs as shown by the results of the lung perfusion test.

The mechanism of deallergization by means of antigen injections eliciting distinct although slight anaphylactic manifestations in contrast to the classic skeptophylactic methods may be explained by the following hypothesis.

Recovery from even a mild macroshock brings about a temporary saturation of the antibodies of the primary shock tissues (e.g. in the lungs). In addition as will be described below this prepares for an alteration in all antibody containing tissues so that the further administration of antigen results at least for a certain time in a state of total deallergization. This may be demonstrated by the absence of antibodies in the blood serum by the absence of the specific uterine reaction in the Schultz Dale experiment and by the negative outcome of the lung perfusion experiment.

3 DEALLERGIZATION BY SPECIFIC SKEPTOPHYLACTIC METHODS ACTING THROUGH MICROSHOCKS

As is well known the skeptophylactic method according to Besredka³⁹⁷ (see above) achieves clinical insensitiveness (so called anti anaphylaxis) by means of intravenous intra spinal intrapentoneal subcutaneous rectal or oral administration of antigens. It is important to note that the manner in which the antigen is administered (whether parenterally or

orally) determines the mode and duration of the protection.

a) SKEPTOPHYLACTIC DEALLERGIZATION BY THE PARENTERAL ROUTE

Proof that the parenteral skeptophylactic methods give rise to a deallergization although only partial and temporary rather than to a condition of temporary hyposensitization is to be found in the following animal experiments.

When an animal previously treated by skeptophylactic methods is again allergized this time passively by means of specific antiserum it has been shown by Weil and Coca³⁹⁸ that the same quantity of antiserum must be used as would have been necessary to render an unprepared guinea pig anaphylactic.

There is further proof of deallergization rather than of hyposensitization in guinea pigs so prepared and clinically refractory to anaphylactic shock. We³⁹⁶ found that in the course of the lung perfusion experiment the lungs of these animals did not react in any way (Figs 23-24). Nevertheless we may speak only of a partial deallergization in the case of animals thus prepared for their uterus still manifested a clear cut specific antigen sensitiveness and the hypersensitiveness could be passively transferred by the blood serum.

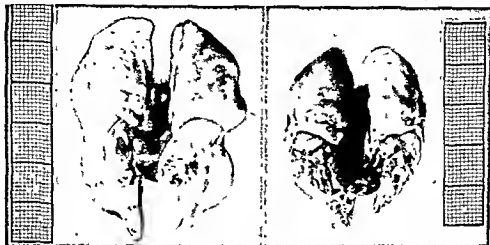
We should like to explain this striking occurrence in the following manner. The principal shock organ of the guinea pig—i.e. the bronchioles and the lungs—possesses a greater avidity for the antigen than does the uterus provided the antigen is administered intravenously in less than shocking doses. It is in the lungs therefore that the first antigen antibody reaction takes place; this is followed by antibody saturation as demonstrated by the negative outcome of the lung perfusion experiment. Under certain conditions (see below) this partial and temporary deallergization can be converted into a state of total and permanent deallergization.

The deallergization of shock tissues by skeptophylactic measures can be demonstrated not only *in vivo* but also *in vitro*. If we add to a uterine horn of an egg white-sensitized guinea pig a 1:10,000 dilution of egg white there will be an immediate reaction under the Schultz

³⁹⁷WEIL R. and COCA A. *Ztschr. f. Immun. u. exp. Med.*
The ap 17 141 1933

Dale's technic. Using the other uterine horn, but adding the egg white in a very dilute form, e.g., 1:1,000,000, and slowly increasing the concentration to 1:200, there will be no anaphylactic reaction of the smooth muscle at all, showing that complete antibody saturation has taken place (FIG. 25).

strated by Besredka, that a period of about two days is necessary to achieve skeptophylactic deallergization of the guinea pig by means of oral administration of the antigen. Furthermore, we noted the interesting result that animals protected in this manner must be considered completely deallergized—as evidenced



LUNG PERFUSION TEST

FIG. 23 Positive result maximally expanded lung of guinea pig allergized to horse serum after anaphylactic shock due to introduction of specific antigen

FIG. 24 Negative result no response of lung of allergized guinea pig deallergized by skeptophylactic method

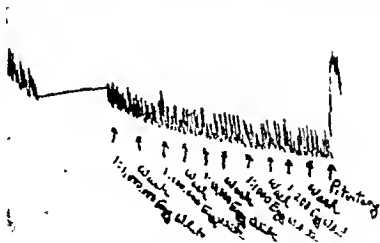


FIG. 25 DEALLERGIZATION BY SKEPTOPHYLACTIC METHOD

In Schultz-Dale test, uterine horn of guinea pig allergized to egg white will not react to concentration of 1:200, provided this is reached gradually. Control horn reacted readily to 1:10,000 dilution.

When deallergized in this manner, the uterus will preserve its specific insensitiveness for the duration of its viability.

b) SKEPTOPHYLACTIC DEALLERGIZATION BY THE ORAL ROUTE

In numerous experiments with a great variety of antigens, we have shown, as first demon-

strated by Besredka, that a period of about two days is necessary to achieve skeptophylactic deallergization of the guinea pig by means of oral administration of the antigen. Furthermore, we noted the interesting result that animals protected in this manner must be considered completely deallergized—as evidenced

by the absence of reactions not only in their principal shock organ (the lung) but also in the uterus, and by the failure of passive transfer. In this connection, it is interesting to note how the organism protects itself against allergization by ingested protein. Feeding of a new food, for example soy bean protein, to an infant is followed by the appearance of antibodies, as

demonstrated by a positive intracutaneous test (Hill³⁹⁹). However, if the food is given continuously to the child, allergic manifestations will only very occasionally be induced by this protein. The explanation may be found in the experiments of Hartley.⁴⁰⁰ When guinea pigs were fed crystalline egg albumin the antibody titer of the serum reached a maximum in from three to five weeks, remained at this level one or two months, and then slowly decreased until it became negative. This approach is, therefore, a deallergization by the oral route, and may serve to elucidate the mechanism in the corresponding situation in human beings.

We offer the following working hypothesis to explain how skeptophylactic preparation by either route succeeds in rendering tissue antibodies incapable of reacting at least in the principal shock organs. The appropriate administration of small quantities of antigen elicits so called microshocks—i.e., antigen antibody reactions—that, although clinically not perceptible, do suffice temporarily to bind the tissue antibodies. Newly formed antibodies are then, in turn, satiated by antigen either repeatedly administered at short intervals by the parenteral route, or slowly absorbed from the gastro intestinal tract when the oral route is used. However, we should not like to consider this glutting as a merely quantitative chemical process, we are of the opinion rather that the microshock goes so far as to cause an alteration in the reactivity of the antibody-forming organs. In other words the microshock is followed not only by loss of antibodies owing to saturation, but also by an arrest of antibody production, thus transforming an allergic organism into one having a normal sensitivity.

It is very interesting to note that skepto-

phylactic intravenous injections, performed at short intervals bring about a state of deallergization that is only partial—i.e. is limited to the principal shock organ. On the contrary, administration by mouth with slow saturation by antigens, brings about a state of total deallergization. In both cases, parenteral or oral deallergization is at first only temporary. However, the peroral method when systematically followed for a period of from one to two weeks leads to a state of permanent deallergization.

The investigations of Dale³⁶⁴ and Brack,⁴⁰¹ as well as our own studies permit the conclusion that deallergization can be achieved not only specifically but also heterospecifically. We consider as hetero antigens, first, group specific antigens and, second, substances of known antigenic character. As in specific deallergization the measures employed in heterospecific deallergization consist of massive doses of the antigen, of injections eliciting mild macroshocks, and of skeptophylactic preparatory administration of antigen (intravenously or by mouth).

As an example of the group specific antigens, timothy pollen extract is often used in the treatment of allergy due to other grass pollens. Similarly we succeeded in treating guinea pigs allergic to horse serum with appropriate doses of pig serum—employing both the technic of massive doses and skeptophylactic administration—with the result that the animals were able to tolerate otherwise lethal doses of horse serum. The same result was obtained in guinea pigs that were hypersensitive to pollen by treatment with pollen from closely related and even from botanically unrelated plants. Substances of known heterospecific antigenicity are exemplified by peptones, tuberculin, etc., the anti allergic effects of which have long been recognized.

³⁹⁹ HILL L. W. J. Allergy 13: 366, 1942.

⁴⁰⁰ HARTLEY G. JR. J. Immunol. 43: 297, 1942.

⁴⁰¹ BRACK W. Ztsch. f. Immunforsch. u. exper. Therap. 34: 407, 1921.

CHAPTER VII

PATHOLOGY OF TISSUES AND BLOOD IN ALLERGY

IN THIS chapter we shall consider only the principal pathologic changes in the tissues characteristic of allergy, without describing the macro- and microscopic findings in the various allergic diseases, which will be found elsewhere under the appropriate headings.

A. PATHOLOGIC ANATOMY

Let us consider first the allergy of infection. As is well known, the allergic tissue reaction depends on the existing state of immunity of the infected organism—granting the same number and virulence of the bacteria. Three general types can be recognized: (1) when immunity is lacking, the incubation period is longer but the disease rapidly leads to death, (2) in the case of moderate immunity, reinfection soon brings on an apparently severe and extensive disease of the organ, though with a tendency to healing; (3) when immunity is strong, the disease germs are rapidly eliminated before they have an opportunity to gain a foothold, but repeated contact with the infectious agents leads to reactions that are to be regarded as the expression of an alteration in the tissues.

In the course of his studies on tuberculosis, Lewandowsky¹⁷¹³ was able to offer experimental proof that when the tubercle bacilli multiplied without restraint, there followed an acute and so-called nonspecific inflammation in the tissue, while, on the other hand, a tuberculoid structure appeared when the bacilli were being gradually destroyed by the organism's biologic defense mechanism. Similar conditions are found in syphilis, deep trichophytosis, blastomycosis, sporotrichosis, etc. (J. Jadassohn, Rame).

We must differentiate between two types of tissue response in infectious allergy: the tuberculoid and the granulomatous structures. The tuberculoid structure is the organism's reactive reply to certain chronically active infectious agents, whereas the granuloma-like foci represent the immune-biologic response of the tissue to certain bacteria, such as streptococci and pneumococci, as well as to foreign protein. An illustration is Bieling's²¹⁵ experiment with

horses that had received subcutaneous injections of strepto-, pneumo-, or meningococci for the purpose of producing immune serums. When these horses subsequently received intravenous injections of the bacteria, inflammation of the joints and thrombotic endocarditis appeared. Klinge⁴⁰² was able to produce a similar endocarditis as well as a myocarditis by repeated injections of protein into the joints. In the same way Roulet succeeded in producing granuloma-like lesions in the pleura of allergized animals.

According to Klinge, the so-called Aschoff bodies, the granulomata pathognomonic for rheumatic infection, represent only a later stage in the process of infectious allergy. This stage is preceded, he claims, by an early fibrinoid infiltration that is characterized microscopically by fibrinoid homogenization of the collagenous connective tissue (see further details under histopathology below, and under rheumatic and rheumatoid joint diseases in Part Three).

We shall now consider the morphologic form of allergic or, as Roessle⁷ has called it, *hyperergic inflammation*. This term is intended to designate an inflammatory process produced by an antigen in an allergized organism. Since hyperergic inflammation can be caused specifically (allergically) and nonspecifically (pathergically), we suggest differentiating between the two by calling them *allergic-hyperergic* and *pathergic-hyperergic* inflammations. We should like to stress the point here that not every hyperergic tissue reaction need necessarily be of an inflammatory nature: as proof of this there are the allergic reactions of isolated surviving organs that serve as the basis for the Schultz-Dale experiment.

In general, the morphologic pictures produced vary, depending on whether an antigen affects a normal (normergic) organism, or one that is in an altered state of reactivity as the result of a previous effect of the same antigen (allergic organism). The Arthus phenomenon represents the classic example and also the

⁴⁰² KLINGE, F. *Der Rheumatismus*. Berlin: Springer, 1933.

highest degree of local allergic hyperergic inflammation. These processes can best be demonstrated in serum allergic frogs (Froehlich). The specific antigen is applied to the mesentery of the small intestine under the microscope one can then see—in contrast to the picture presented in control experiments with normergic frogs—the development of an unusually rapid severe inflammatory process (Fig. 26). These responses are apparently all concerned with the blockade of the foreign substance: the local circulation comes to an instant halt as a result of arteriolar contraction fol-

lowed by formation of a zone of capillaries free from erythrocytes (serous stasis) as well as of a zone of edema and leucocyte migration. Similar observations were made on the arterioles, capillaries, and venules of the rabbit's ear by Abell and Schenck.⁴⁰³

fact that homogenization of the collagenous tissue begins at the immediate site of the injection.

This fibrinoid homogenization of the connective tissue was subsequently regarded by Klinge, Roessle, and their schools as the pathognomonic sign of allergic inflammation. But Aschoff, Graff, and others emphatically disagree with this viewpoint. They point out that the employment of weak doses on allergized animals leads to a rapid and severe local response, but not to a fibrinoid reaction of the connective tissue. On the other hand, it is pos-

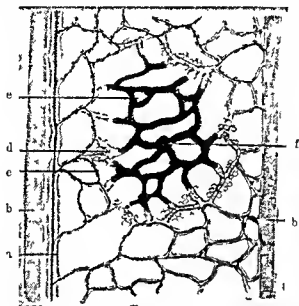


FIG. 26 ALLERGIC HYPERERGIC INFLAMMATION OF MESENTERIC VESSELS OF ALLERGIZED FROG (D. AGRAM).
a = artery b = veins c = capillaries with central current d = zone of plasma filled capillaries and leucocyte migration e = zone of stasis f = site of contact with antigen (After R. Roessle)

sible to evoke a fibrinoid homogenization with the first injection of a protein containing substance—at a time when allergization could not have occurred. Schmidtman, Werner, Siegmund, and others have shown that homogenization of the collagenous fibers can be brought about by all manner of injury, whether of physical, chemical, or infectious toxic nature.

In conclusion, we should like to say there fore that it is by no means permissible to assume the presence of an allergic hyperergic inflammation solely on the basis of a fibrinoid homogenization.

⁴⁰³ ABELL, R. G. and SCHENCK, H. P. *J. Immunol.* 34: 19, 1938.

B. HISTOPATHOLOGY

Berger and Lang¹⁰¹ studied allergic reactions elicited both actively and passively at the height of wheal formation and again seven hours later. The histologic pictures were substantially the same, regardless of the method of production. Likewise, there is a definite conformity with the milder degrees of local anaphylaxis. This constitutes the histologic evidence of the basic identity of anaphylaxis and allergy.

The histopathology of the allergic reaction is characterized principally by (1) rapid and violent onset, (2) capillary dilatation, stasis of the blood column, and edema, (3) infiltration of leucocytes, and (4) marked concentration of eosinophile cells.

At the height of the wheal formation, Berger and Lang found marked edema of the connective tissue, as well as homogenization of the collagenous bundles, hyperemia, chemotaxis, marked migration of the leucocytes, and formation of leucocytic sheets around the vessels, with excessive predominance of eosinophils. They also found that seven hours later, when the macroscopic changes had almost disappeared, the microscopic manifestations were still quite pronounced.

Kline, Cohen, and Rudolph¹⁰² studied the skin reactions they had elicited in hypersensitive individuals and in control subjects by injections of pollen and dust or by exposure to cold and heat. It was seen that in allergic individuals these exposures evoked the prompt appearance of an inflammation of the cutis and subcutis. Examination during the first ten minutes and then again after three hours showed that these changes were very similar to those seen in ordinary inflammations, although less intense. On the other hand, it was seen that during a period of from fifteen to thirty-five minutes following the injections or exposures, 25 to 50 per cent of the leucocytes were eosinophilic.

In the production of experimental dermatitis by means of 2,4-dinitrochlorobenzene, Mom, Noussiton, and Leon¹⁰³ found that the histo-

logic pictures and the sequence of the changes were identical, whether specific sensitization existed or not. This accords with the observation that toxic and allergic contact dermatitides are by and large morphologically indistinguishable, and may perhaps be explained by the fact that the skin is limited in the variety of ways in which it can respond to inflammation. As might be expected, it was found that subjects with an allergic predisposition showed an exaggeration and acceleration of the reaction, although the response was otherwise similar.

C EOSINOPHILIA IN TISSUE AND BLOOD

The presence of blood eosinophilia is considered to be a characteristic sign of the allergic diseases. But the symptom of blood as well as tissue eosinophilia is found not only in allergic diseases but also in numerous other conditions, such as parasitic infestations, especially trichinosis and hookworm, leucemia and other blood dyscrasias, lymphoblastomatosis, scarlatina in the acute stage, in postinfectious and post toxic conditions, in certain acute diseases of the muscles, and sometimes even as a family characteristic. It is occasionally seen in malignancies, especially with metastatic involvement of the liver, syphilis, pleural effusions, benzene poisoning, and eosinophilic granuloma of bone, and also following digitalis therapy and the ingestion or injection of liver. In a review of 418 cases with a blood eosinophilia of 6 per cent or more, Stickney and Heck¹⁰⁴ found respiratory allergy to be the commonest single cause, followed in order of frequency by various dermatoses, acute and chronic infections, including acute appendicitis, chronic ulcerative colitis, chronic cholecystitis, and infectious arthritis, malignancies, diseases of the reticulo-endothelial system, and portal cirrhosis or other conditions with liver damage. A very high degree of eosinophilia (20 per cent or over) is rarely caused by the usual types of allergy (except in drug allergies, particularly arsphenamine dermatitis, where we have seen eosinophil counts up to 75 per cent), and it is well to consider the possibility under these circumstances of blood dyscrasias,

¹⁰¹ BERGER, W., and LANG, F. J. Beitr. z path. Anat. u. allg. Path. 87, 71, 1931

¹⁰² KLINE, B. S., COHEN, M. B., and RUDOLPH, J. A. J. Allergy 3: 551, 1932

¹⁰³ MOM, A. M., NOUSSITON, F., and LEON, R. C. Rev. argent. dermatol. 17: 321, 1945

¹⁰⁴ STICKNEY, J. M., and HECK, F. J. M. Clin. North America 21, 915, 1944

periarthritis nodosa, and transient pulmonary infiltration. It is not permissible, therefore, to consider blood or tissue eosinophilia per se as conclusive evidence of the existence of an allergy.

Accurate determination of the number of circulating eosinophils may be enhanced by employing a specially prepared white cell diluting fluid, by means of which the eosinophils may be counted directly in the counting chamber without resorting to stained films (Randolph⁴⁰). This diluent consists of 0.25 per cent phloxine and 0.25 per cent methylene blue dissolved in equal parts of propylene glycol and water, and must be freshly prepared from stock solutions about every four hours.

According to Nikolaeff and Goldberg, the leucocyte formula of an allergized animal changes in the direction of an increase in the number of monocytes and eosinophils. During an anaphylactic shock, however, there is a high monocyte count and a decrease in the number of eosinophils, after the shock is over, there is a decrease in the number of monocytes and an increase in eosinophils. During acute allergic attacks in human beings also, it has frequently been observed that an existing hypereosinophilia of the blood is replaced by a state of aneosinophilia (Piness, Uffenheimer, Becker, Deamer), simultaneously, there is an increase of the eosinophile cells in the sternal bone marrow (Debre, Lanny, and Bernard), as well as in the products of allergic reactions (e.g., sputum in asthma, nasal secretion in allergic rhinitis, mucous shreds in allergic colitis). When the allergic attack has passed, the eosinophils in the blood relatively soon begin to increase again. Randolph and Rawling⁴¹ found similar changes in the leucocyte response to the trial ingestion of a single small dose of sulfonamide in three asthmatics known to be sensitive to the drug. Dalton and Selye report a similar decrease and subsequent increase in blood eosinophilia during the "alarm reaction" in rats and rabbits. The alarm reaction is the response to a variety of damaging stimuli not, of course, of allergic nature. W. Jadassohn has shown that primary urticariogenic stimuli

(e.g., stroking of the skin, intracutaneous injections of morphine, codeine, histamine, etc.) elicit, in nonallergic individuals, urticarial reactions that contain eosinophile cells in about the same proportion as seen in wheals elicited in hypersensitive individuals by the action of allergens. Ishihara states that blood eosinophilia is produced by injections of heterologous antigen in sensitized guinea pigs, even when anaphylactic reactions are not evoked. In this connection it might be interesting to note Griebel's comments on the meteorologic and seasonal fluctuations in the blood eosinophilia.

In view of all these facts, the most that can be said is that blood eosinophilia must be regarded as the result either of a nonspecific stimulation or of a specific allergic reaction.

With regard to *tissue eosinophilia*, however, the evidence seems more strongly to indicate a preceding allergic reaction. This view is supported mainly by the appearance of eosinophile cells in the secretions from the conjunctiva, nose, bronchi, colon, or vagina, or in the urine. Numerous authors (Cooke,⁴² Hansel^{32a} and others) are of the opinion that these eosinophile cells appearing in secretions or excretions are of histogenic nature, and do not originate in the blood. The investigations of Salari and Guarneri also suggest the local origin of eosinophils. These authors found that the increase of eosinophils is more pronounced in the blood taken from an arm on which cutaneous tests have been performed.

Burkhart and Montgomery⁴³ showed that patients with a high percentage of eosinophils in the blood are more apt to have a local tissue eosinophilia after an injection of foreign protein than are those with a normal or low percentage. This was especially true in cases of neurodermatitis and dermatitis herpetiformis. The binuclear usually predominated over the mononuclear eosinophils in the tissue infiltrates.

Exceptional conditions with regard to tissue eosinophilia are to be found in periarthritis nodosa, as well as in the disease picture described by Harkavy, of eosinophilic pleural and

⁴⁰ RANDOLPH, T. G. *J. Allergy* 13: 89, 1934.

⁴¹ Idem and RAWLING, F. F. *ibid.* 16: 17, 1935.

⁴² COOKE, R. A. *Am. J. N. Sc.* 133: 309, 1932.

⁴³ BURKHART, R. J. and MONTGOMERY, H. *Arch. Dermat. & Syph.* 49: 19, 1934.

peritoneal exudates in connection with asthma. These conditions will be discussed in the relevant chapters (pp. 832, 588).

In conclusion it may be said that blood and tissue eosinophilia frequently accompany allergic diseases—without, however, permitting us to assume that a high eosinophil blood count proves the existence of a state of hypersensitivity, or that its relative height reflects the severity of an allergic reaction. Furthermore, according to the present consensus, the eosinophilia itself is less important than fluctuations in the eosinophil curve. It is recommended, therefore, that such blood examinations be systematically continued for some time. Romberg as well as Hajós is of the opinion that the absence of eosinophile cells during immunization therapy is to be regarded as an unfavorable sign, since it points to a diminished reactivity on the part of the organism. Although no conclusive proof is available, it is now generally believed that the eosinophile cells participate in the defense processes of the human body, especially in conditions of hypersensitivity.

D. CLINICAL PATHOLOGY

It is noteworthy that remarkably few changes in the blood are to be found even in severe allergic manifestations. This does not apply, of course, to acute anaphylactic shock, in which typical alterations appear (p. 87).

The number and color of the red corpuscles are rarely altered. Concentration of the blood has been observed in allergic attacks and in artificially induced hay fever (Bray; Black and Kemp). This is probably explained by the transudation of the serum into the tissues. Mayer and Fleischer found an inconstant increase in blood osmotic pressure in anaphylactic rabbits. There is a difference of opinion as to whether the blood coagulation time is shortened or prolonged. Opinions also differ as to the behavior of the sedimentation rate. At any rate, the present writers are in agreement with a number of other authors (Schulhof; Ellis; Westcott and Spain) in believing that sedimentation is retarded in allergic diseases, provided they are not complicated by infection.

As Widal and his co-workers⁴¹² have shown, adequate contact with a specific allergen will cause the allergic organism to respond with the development of a very definite blood picture known as the *hemoclastic crisis*. This is characterized by a decrease in the leucocyte count, relative lymphocytosis, a decrease in the protein colloids, an increase in blood coagulability, lowered blood pressure, and sometimes a rise in temperature, and albuminuria. The most favorable moment for this examination is from twenty to thirty minutes after the administration of the allergen, after an hour or so, conditions become normal again. On the basis of extensive investigations, the present opinion is that the hemoclastic crisis represents a symptom in coordination with the clinical manifestations. These changes result from a disturbance in the colloidal equilibrium, following the neutralization of antibodies in the blood by the administered allergen. Other authors are of the opinion that a positive outcome of this test merely indicates an intense irritation of the autonomic nervous system, or that it is especially prone to irritation, generally or specifically, by a given irritant.

A similar principle is the basis of the *leucopenic index* Vaughan,²¹ who developed this method, defined the index as representing the relationship between the fasting leucocyte count and that after digestion. According to this test, allergic hypersensitivity to a food is considered to exist if its ingestion is followed by a significant fall (2,000 cells) in the total leucocyte count. (For further details, see p. 194)

According to Joltrau, the modification of the *leucocytic formula* in allergic reactions is characterized by a decrease in the number of neutrophils, with a relative increase of the mononuclear cells; in cases of acute infection, on the other hand, an increase in the white count is marked by a decrease in the number of monocytes as well as of eosinophils. For further information about the white cell and differential count of the blood, see the preceding section.

The *refractive index* of the serum is lowered during allergic reactions in 85 per cent of cases,

⁴¹² WIDAL, F., AZARI, P., BEISSACQ, E., and JOLTRAU, E.: Bull. et mém. Soc. med. d. hôp. de Paris 37, 293, 1911

elevated in 10 per cent and unchanged in the remaining 5 per cent (Bray)

The systolic *blood pressure* of allergic individuals is often subnormal (90 to 120 mm of mercury) During asthmatic attacks the blood pressure may be increased occasionally however it is decreased

Friedberger and others have shown in animal experiments that the union of antigen and antibody *in vitro* or *in vivo* results in a disappearance of the complement Veil and Bucholz

Schnabel and Paul and Pely have recently assumed that a low or absent complement titer indicates the presence of an allergic disease and that an alteration in the colloidal state of the blood may be postulated This in turn is said to depend upon some hepatic dysfunction According to Deutsch and Weiss and to our own investigations it is not possible to demonstrate a lowered or lacking complement titer in the majority of cases—even in allergic diseases presenting very severe manifestations

CHEMISTRY OF ALLERGY

EVERY biologic process is accompanied by local and, under certain circumstances, by general chemical alterations (e.g., changes in the pH, in the cation content of the blood and tissues, in the water metabolism, etc.). This question is not to be confused, however, with the problem as to whether chemical or physical disturbances of humoral or cellular character are capable of evoking the manifestations known as anaphylaxis or allergy. As is well known, Richet established the so-called anaphylatoxin theory, intended to explain the onset of anaphylaxis as the result of a poison created by the union of antigen and antibodies. This assumption proved to be no more tenable than the belief that a "poison" that elicits the shock is set free from the precipitate (in the course of the antigen-antibody interaction) by the influence of the complement (Friedberger, Bordet), or than the hypothesis that it is derived from protein by proteolytic processes in the course of parenteral digestion (V. Vaughan).

During the past thirty years, the histamine theory has generally gained dominance, and this, in turn, has recently been challenged by the acetylcholine hypothesis.

A. THE HISTAMINE AND ACETYLCHOLINE THEORIES

Histamine, beta-iminazolyethylamine, is a derivative of the amino acid histidine, and is a normal constituent of nearly all mammalian tissues, including the blood, but in bound, inactive form. It is also found in the granular leucocytes and particularly in the eosinophils. The nature of the binding of histamine with the cell constituents is still unknown, but is probably in the form of peptide bonds with the amino acid chains which constitute the protein of the cells (Rocha e Silva⁴¹³). It can also be formed in the intestinal tract by decarboxylation of histidine through the action of certain bacteria. Dale and Laidlaw⁴¹⁴ called attention

to the fact that histamine, when injected into normal animals, causes the typical symptoms and pathology of anaphylactic shock: the guinea pig responds with bronchial constriction, the rabbit with contraction of the pulmonary arteries, the dog with engorgement of the liver, due to constriction of the hepatic veins. In human beings injection of histamine produces a marked fall in blood pressure, vasodilatation, increased permeability of the peripheral capillaries, and an urticarial wheal at the site of injection.

Lewis⁴¹⁵ states that the so-called triple response—occurring after injury to the skin by physical, thermal, or chemical agents—is identical with the reaction resulting from intradermal injection of histamine. This response consists of (1) local capillary dilatation at the site of injury, (2) escape of protein-rich fluid through the more permeable capillaries, causing a wheal, and (3) reflex dilatation of the arterioles, with the appearance of an irregular flare.

Recent reviews evaluating the significance of histamine in the mechanism of anaphylactic and allergic reactions have been contributed by Code,⁴¹⁶ Rocha e Silva,⁴¹⁶ and Dragstedt.⁴¹⁷ There can be little doubt that histamine is intimately connected with allergic phenomena, but opinions vary greatly as to whether it is essential thereto, and as to how much of the clinical picture is due directly to it. A quantitative method for the estimation of histamine in the blood (Code's modification⁴¹⁸ of the technic of Barsoum and Gaddum) has increased our understanding of its rôle.

We shall mention only a few of the studies that endeavor to prove that the antigen-antibody reaction leads to cellular production of histamine or of a substance with histamine-like action (H substance of Lewis), and that this substance irritates the cells. Bartosch and his

⁴¹³ LEWIS, T. *Blood Vessels of Human Skin and Their Responses*. London: Shaw, 1927.

⁴¹⁴ ROCHA E SILVA, M. *J. Allergy* 15: 399, 1941.

⁴¹⁵ DRAGSTEDT, C. A. *ibid.* 16: 69, 1945.

⁴¹⁶ CODE, C. F. *J. Physiol.* 89: 257, 1937.

⁴¹⁷ ROCHA E SILVA, M. *J. Pharmacol. & Exper. Therap.* 77: 198, 1943.

⁴¹⁸ DALE, H. H., and LAIDLAW, P. P. *J. Physiol.* 41: 318, 1911.

associates flooded the lungs of sensitized guinea pigs with antigen and demonstrated the subsequent release of a substance possessing histamine-like action. Dragstedt and Mead reported that in experiments on dogs, the amount of histamine liberated during anaphylactic shock was sufficient to account for the severity of the reaction. It has been shown also *in vitro* that when blood cells from sensitized animals come into contact with the antigen histamine is released into the plasma in sufficient quantity to be physiologically active and to play a definite role in anaphylactic shock (Katz and Cohn,⁴¹⁹ Rose and Browne⁴²⁰). Farmer claims that sensitized guinea pigs can be nonspecifically desensitized by injection or oral administration of histamine, and concludes that histamine is the substance responsible for the anaphylactic contraction of smooth muscle. However, Essex and Horton⁴²¹ found that the protection afforded these animals by pretreatment with histamine was not great, and Courtright, Hurwitz, and Courtright⁴²² that histamine and acetylcholine both alone and together, had no significant delaying or preventing action against sublethal anaphylaxis by the inhalation method.

In reviewing the evidence for and against the intervention of histamine in anaphylaxis, Dragstedt⁴¹⁷ concludes that it is a definite factor, although the mechanism by which it is released from the tissues is not understood. Rocha e Silva and Andrade⁴²³ showed that it can be released by the action of such enzymes as trypsin and papain *in vitro*. The emphasis on histamine is illustrated by Albus' suggestion⁴²⁴ that the term "histamine susceptible constitution" be substituted for "allergic constitution." However, Farmer⁴²⁵ has shown that the intradermal test with histamine is not of value in differentiating allergic individuals from non allergic, even if Atkinson's criteria⁴²⁶ are reduced. While not denying the importance of histamine, he points out that there is

no convincing evidence that allergic patients are simply more sensitive to it than are normal individuals.

Histamine taken orally is promptly absorbed and exerts its pharmacologic effects, and may in allergic patients produce the specific symptoms. It has been successfully used by this route in the treatment of allergic rhinopathy by Gant, Savignac and Hochwald.⁴²⁷

The complexities of the problem are well illustrated by the following. Since histidine is the main source from which histamine is derived in the body, Dragstedt⁴²⁸ suggests that a histidine free diet be given. However, histidine (along with tyrosine, methionine, arginine, and choline) is antagonistic to the action of histamine in animals. Hence Ruskin⁴²⁹ concludes that histidine may be therapeutically useful in allergic conditions. A great deal of basic investigative work will be required before such contradictions can be reconciled.

Some authors hold that the prophylactic and therapeutic efficacy claimed for histaminase in certain allergic disorders constitutes some proof that these may be attributable to inadequate detoxification of histamine formed in the alimentary tract or elsewhere within the organism. Histaminase is the name given by Best and McHenry to a histamine-inactivating substance, probably of enzyme character, present in various tissues, especially the kidneys and small intestine. Karady and Browne⁴³⁰ report that histamine formation and anaphylactic shock were effectively prevented in guinea pigs by parenteral preadministration of histaminase. These findings were corroborated by Barlow and Homburger,⁴³¹ using both the oral and parenteral routes of administration of histaminase, but were refuted by Best and McHenry.⁴³² Rose and Browne,⁴²⁰ Alexander and Bottom,⁴³³ and Courtright et al.⁴³⁴

Foshay and Hagebusch⁴³⁵ and Cherry and Prickman⁴³⁵ demonstrated the prophylactic

⁴¹⁹ KATZ C. and COHN S. J. A. M. A. 117: 1282, 1941.

⁴²⁰ ROSE B. and BROWNE J. S. L. J. Immunol. 41: 403, 1941.

⁴²¹ ESSEX H. E. and HORTON B. T. Proc. Staff Meet. Mayo Clin. 16: 603, 1941.

⁴²² COURTRIGHT L. J., HURWITZ S. R. and COURTRIGHT A. B. J. Allergy 13: 444, 1942.

⁴²³ ROCHA E SILVA M. and ANDRADE S. O. J. E. of Chem. 149: 9, 1943.

⁴²⁴ ALBUS G. Ztsch. f. d. ges. exper. Med. 108: 592, 1941.

⁴²⁵ FARMER L. J. Allergy 16: 44, 1945.

⁴²⁶ ATKINSON M. J. A. M. A. 116: 1753, 1941.

⁴²⁷ GANT J. C., SAVIGNAC R. J. and HOCHWALD A. New England J. Med. 229: 579, 1943.

⁴²⁸ DRAGSTEDT C. A. Quart. Bull. Northwestern Univ. M. School 17: 102, 1943.

⁴²⁹ RUSKIN S. L. Am. J. Digest. Dis. 11: 209, 1943.

⁴³⁰ KARADY S. and BROWNE J. S. L. J. Immunol. 37: 463, 1939.

⁴³¹ BARLOW O. W. and HOMBURGER E. J. Allergy 12: 346, 1941.

⁴³² BEST C. H. and McHENRY F. W. Canad. M. A. J. 43: 163, 1940.

⁴³³ ALEXANDER H. L. and BOTTOM D. J. Immunol. 39: 457, 1940.

⁴³⁴ FOSHAY L. and HAGEBUSCH O. E. J. A. M. A. 112: 2398, 1937.

⁴³⁵ CHERRY J. H. and PRICKMAN L. E. Proc. Staff Meet. Mayo Clin. 16: 38, 1941.

value for man of histaminase given prior to the administration of serum, and the symptomatic relief of serum sickness when histaminase therapy is instituted during the first three days of symptoms. Roth and Horton,⁴³⁶ Vaisberg,⁴³⁷ Goodson,⁴³⁸ and others report favorably on the prophylactic and therapeutic action of histaminase in physical allergies, and Taylor and Hilger⁴³⁹ similarly respecting hypersensitiveness to liver extract. Laymon and Cumming, Goldberg, and others report good results in various cutaneous disorders presumed to be of allergic origin.

Similarly, the protection of allergized animals against anaphylaxis and the therapeutic results claimed for histamine-azoprotein (Hapamine) have been advanced as confirmation of the histamine theory of allergy. This substance represents a conjugate protein antigen, capable of stimulating the formation of antibodies (including precipitins) specific for histamine (Cohen and Friedman⁴⁴⁰). By this means, animals were rendered refractory to histamine and displayed a decided degree of resistance to anaphylaxis (Fell, Rodney, and Marshall⁴⁴¹). Histamine-azoprotein has been employed clinically by a number of investigators, with some favorable results, although an increasing number of severe anaphylactoid reactions are being reported. Its clinical indications will be considered in chapter XII.

Other antihistamine preparations are being intensively investigated in an attempt both to shed light on the basic mechanisms of allergy and to provide therapeutically useful drugs. Benadryl (β dimethylaminoethyl benzhydryl ether hydrochloride) is a newly synthesized histamine antagonist. Pharmacologic studies on animals suggest that it has three significant actions: it alleviates (1) the bronchial constriction caused by histaminic or anaphylactic shock, (2) the vasodepressor effects of histamine, and (3) smooth muscle spasm. McElin and Horton's^{442a} observations indicate that

benadryl appears to be of considerable promise in the treatment of allergic diseases, particularly of the underlying edema which is thought most probably to be provoked by the local release of histamine or histamine-like substances. Preliminary reports show that benadryl is highly effective in the treatment of urticaria and angioneurotic edema (O'Leary and Farber,²⁷³⁶ Pillsbury,²⁷³⁷ Feinberg and Friedlaender,⁶³² Urbach), particularly urticaria due to physical agents (Feinberg and Friedlaender,⁶³² Urbach) and other forms of physical allergy, and useful in the treatment of hay fever and asthma (Koelsche, Prickman, and Carryer^{443b}), of the syndrome of physical allergy of the head (perennial rhinopathy, myalgia, endolymphatic hydrops of Ménière's disease, and vasodilating pain), especially as regards the component of rhinopathy (Williams^{444c}), and of allergic diseases in childhood (Logan^{445d}).

Other antihistaminic drugs were developed in France by Halpern and others,⁴⁴⁶ and called antergan and neoantergan. They reported success in the treatment of serum sickness, hay fever, urticaria, intolerance to barbiturates, migraine, and less effect in asthma. A series of similar compounds have been studied by Mayer et al.⁴⁴⁷ An excellent discussion of the present knowledge of antihistaminic substances was recently contributed by Code.^{448e}

Despite the many brilliant and persuasive arguments advanced in defense of the histamine theory, it is becoming increasingly apparent that not all allergic manifestations are caused by the liberation of histamine or of histamine-like substances in the tissues. In the first place, two important symptoms regularly seen in anaphylactic shock are absent in histamine shock—namely, the drop in body temperature, and the prolongation of the blood coagulation time (clinically apparent in the incoagulability of the blood). There is reason to think that the latter is due to a release of heparin from the liver (Jacques and Waters³⁶⁷). Wells¹⁶⁰ lists as the chief objections to his-

⁴³⁶ ROTH, G. M., and HORTON, B. T. *ibid* 12: 129, 1937

⁴³⁷ VAISBERG, M. *New York State J. Med.* 39: 2199, 1939

⁴³⁸ GOODSON, W. H., JR. *Proc. Staff Meet., Mayo Clin.* 13: 500, 1938

⁴³⁹ TAYLOR, C. B., and HILGER, D. W. *J. A. M. A.* 117: 1380, 1943.

⁴⁴⁰ COHEN, M. B., and FRIEDMAN, H. J. *J. Allergy* 14: 195, 1943

⁴⁴¹ FELL, N., RODNEY, G., and MARSHALL, D. E. *J. Immunol.* 47: 33, 1943

^{442a} MCELIN, T. W., and HORTON, B. T.: *Proc. Staff Meet., Mayo Clin.* 20: 417, 1945

^{443b} KOELSCH, G. A., PRICKMAN, L. E., and CARRYER, H. M. *ibid* 20: 432, 1945

^{444c} WILLIAMS, H. L. *ibid* 20: 434, 1945

^{445d} LOGAN, G. B. *ibid* 20: 435, 1945

⁴⁴⁶ *Foreign Letters* *J. A. M. A.* 129: 1219, 1945

⁴⁴⁷ MAYER, R. L., HITTNER, C. P., and SCHOLZ, C. R. *Science* 107: 93, 1945

^{448e} CODE, C. F. *Proc. Staff Meet., Mayo Clin.* 20: 439, 1945

mine its failure to desensitize animals and its tendency to produce strong reactions in a specifically desensitized uterine strip. The theory that histamine causes anaphylaxis is further contradicted by the following observations: Heparin inhibits anaphylactic but not histamine reactions (Hyde) and arginine prevents death from histamine but not from anaphylactic shock (Landau and Gay⁴⁵). The sensitized rat uterus contracts on contact with the specific antigen (Kellaway) is relaxed by histamine (Voegtlin and Dyer) but responds to some substance released by sensitized guinea pig lung tissue in the course of an anaphylactic shock (Campbell and Nicoll). Bender⁴³ showed that the iris of a denervated as well as a normal eye contracts in anaphylaxis but not after the intravenous injection of histamine. According to Matron⁴⁴ the intense vasodilatation of the abdominal viscera observed in anaphylactic shock is absent during histamine shock; on the other hand, hyperglycemia is noted in the latter but not in the former. These results seem to indicate that some substance other than histamine is released during anaphylactic shock. Moreover, dogs may die in anaphylactic shock at a time when their blood histamine is at or rapidly approaching normal levels (Code⁴⁶). The central nervous system has never been shown to contain histamine yet it can be the site of typical allergic reactions.

In human beings there is no consistent variation in the histamine content of the blood in allergic patients either between or during attacks (Rose⁴⁶, Rocha e Silva⁴⁶) although they do show considerable fluctuations in their histamine levels as compared with the relatively constant values in normal subjects.

Neither clinically nor histologically can local anaphylaxis be achieved by means of histamine injections (Berger and Lang). Furthermore there is a difference in the histologic pictures of the lungs of animals that die from anaphylactic and histamine shocks; in instances of anaphylactic death there is an overwhelming eosinophilia as well as inflammatory manifestations in instances of histamine shock there

are evidences of circulatory disturbances and of moderate eosinophilia (Kallos and Pagel⁴⁸).

As regards the experimental and therapeutic results obtained by the use of histaminase these have not been invariably confirmed or are explainable in some other way. Thus Best and McHenry⁴³ were unable to confirm the experiments of Karady and Browne⁴⁹ in achieving protection of guinea pigs against anaphylactic and histamine shock by the use of histaminase. The recent animal experiments of Lemley and Laskowski⁴⁶ indicate that the toxicity of histaminase in its present state of development prevents the use of adequate protective dosages. Toomey et al⁴⁷ and Eger and Stone⁴⁸ failed to corroborate the ameliorating effect of histaminase on the urticaria of serum sickness and Peshkin et al⁴⁹ on various allergies in children. A fair presentation of the subject is to be found in a report of the Council on Pharmacy and Chemistry⁵⁰ of the American Medical Association. Some of our own experiments (unpublished) would seem to suggest that certain good therapeutic results might be explained in some cases as due to its effect on a pathologic intestinal flora rather than to a histamine destroying mechanism.

It is obvious from this brief review that the problem as to the etiologic significance of histamine or histamine like substances in allergic phenomena is by no means solved.

In recent years there has been a tendency among investigators to assume that the chemical substance that mediates anaphylaxis or allergy is acetylcholine. This belief has been fostered by the fact that all allergic manifestations can be reproduced by stimulating the parasympathetic nerves with this substance. There is some speculation as to whether this effect is to be explained as due to an excess of acetylcholine to disturbance in its normal breakdown by the choline esterase or to some peculiar hypersensitiveness to this substance. Chigira⁵¹ not only found that acetylcholine

⁴⁵ LANDAU S W and GAY L N. Bull. Johns Hopkins Hosp. 45: 55, 1944.

⁴⁶ BENDER M B. J. Immunol. 47: 453, 1943.

⁴⁷ MATRON P. Compt. rend. Soc. de biol. 132: 42, 1939.

⁴⁸ ROSE B J. Clin. Investigation 20: 419, 1941.

⁴⁹ LEMLEY J M and LASKOWSKI M A. Biochem. 6: 11, 1941.

⁵⁰ TOOMEY J A, KRIEGER F M and EPSTEIN H C. J. Pediat. 24: 290, 1944.

⁵¹ EGER S A and STONE J E. Penn. Acad. Sci. 47: 31, 1943.

⁵² PESHKIN M M, RAFFAPORTI H G, NIESSEN W, FEYER I S, CLELLAN A and BERGER A. J. Pediat. 22: 426, 1943.

⁵³ COUNCIL ON PHARMACY AND CHEMISTRY. Report. J. A. M. A. 115: 1019, 1940.

⁵⁴ CHIGIRA S. Jap. J. Exp. Med. 19: 23, 1942.

shock resembled anaphylactic shock more than did histamine shock, but also that previous treatment of the animals with eserine enhanced both of the first two, but had no effect on histamine shock. Villaret and other French authors found that from 0.02 to 0.04 Gm of pure acetylcholine given to an asthma patient caused an immediate attack, while in normal persons asthma did not occur, except in patients who had recently recovered from pneumonia. It produced asthma in dogs as well, provided the lungs were irritated by exposure to chlorine gas. Foggie⁴² has shown that this substance can cause bronchial constriction in the lungs of a rat. In cases of asthma, the acetylcholine content of the blood is increased (Wenner and Buhrmester⁴³). Attempts made to treat asthma with mecholyl, the stable derivative of acetylcholine, were unsuccessful (Logue and Laws⁴⁴). However, when very small doses (0.01 to 0.05 mg.) were employed by E. B. Abramson and the senior author, encouraging results were obtained in some cases of asthma and rhinopathy.

In opposition to the acetylcholine theory, it has been pointed out that this product is released only by nerve stimulation and not—as in the case of histamine—by tissue injury. No significant liberation of acetylcholine was observed by Farber, Pope, and Landsteiner⁴⁵ from excised tissues of allergized animals shocked *in vitro*. (For further details, see p. 37.)

B. CHEMISTRY OF ALLERGENS

Marrack,⁴⁶ Haurowitz,⁴⁷ Boyd,⁴⁸ and Sevag⁴⁹ have presented excellent and comprehensive reports of the present state of chemical knowledge with regard to antigens and antibodies. Pauling, Campbell, and Pressman⁵⁰

have reviewed the nature of the specific forces between antigen and antibody, and of the precipitin reaction from the point of view of modern chemistry. We shall be able to mention here only a few salient facts.

The specificity of antigens is determined by their chemical structure. Obermayer and Pick were the first to point out that when serum protein is altered by the addition of iodine, for instance, it loses its immunologic type specificity and acquires a new specificity. Wells⁵¹ demonstrated that the chemical constitution of allergens is of greater importance than their biologic origin. Thus, chemically similar proteins of seeds of different genera may have the same anaphylactic action, while, on the other hand, chemically dissimilar protein substances from the same seed possess different anaphylactic properties. Another example is provided by the experiments with the four proteins contained in milk, likewise showing that the chemical constitution is of greater immunologic import than is the biologic origin.

The hypersensitivity may represent a reaction to the molecule as a whole or to certain radicals of the molecule. This is different in each individual case and the precise nature of the hypersensitivity must therefore always be determined by adequate tests. Thus, in the senior writer's⁵² case of resorcin hypersensitivity, the patient was also allergic to the isomeric compounds, breznicatechin and hydrochinone. On the other hand, in Nathan and Stern's case the sensitivity appeared to be strictly bound to the steric structure of the resorcin molecule. Doerr⁵³ mentions cases of iodoform hypersensitivity in which the individuals also reacted to bromoform, thus relating the specific hypersensitivity to the methyl radical. In the quinine cases of Dawson and Gabade,⁵⁴ the allergy extended to levorotatory alkaloids such as ethylhydrocupreine and cinchonidine, but not to dextro-rotatory isomers such as quinine and cinchonine. In sensitivity to acetylsalicylic acid (aspirin), one finds persons allergic only to the whole complex; some who are sensitive to the acetyl radical; some, to salicylates; and some, to any two or three of these chemical groupings. There are cases of sensitivity to species-

⁴² FOGGIE, P. *Quart J Exper Physiol* 26: 225, 1937.

⁴³ WENNER, W. F., and BUHRMESTER, C. C. *J Allergy* 9: 85, 1937.

⁴⁴ LOGUE, R. B., and LAWS, C. *ibid* 13: 414, 1912.

⁴⁵ FARBER, S., POPE, A., and LANDSTEINER, E. *Jr Arch Path* 37: 275, 1944.

⁴⁶ MARRACK, J. R. *The Chemistry of Antigens and Antibodies*. Med Research Council, Sp Rep ser. no 230. London His Majesty's Stat Off., 1938.

⁴⁷ HAUROWITZ, F. *Chemie der Antigene und der Antikörper*. In Kalló, P. (ed.) *Fortschritte der Allergielehre*, New York Karger, 1939.

⁴⁸ BOYD, W. C. In *Colloid Chemistry*, ed by ALEXANDER, J. New York Reinhold Pub Corp., 1944.

⁴⁹ SEVAG, M. G. *Immuno-Catalysis*. Springfield Thomas, 1945.

⁵⁰ PAULING, L., CAMPBELL, D. H., and PRESSMAN, D. *Physiol Rev* 23: 155, 1943.

⁵¹ DAWSON, R. T., and GABADE, F. A. *J A M A* 91: 701, 1929.

specific fractions of lactalbumin or to caseins. The specificity may be of such a high degree that a person may be sensitive only to straw berries grown in certain districts or to oranges grown in only one section of the country or only to honey derived from linden blossoms and not to honey from heath flowers.

Only the proteins with relatively high molecular weights (albumin globulin pseudo globulin euglobulin etc.) can act as allergens. Jones and Fleisher as well as Stull, Sherman and Cooke state that the constituent of serum most active in the causation of symptoms is pseudoglobulin. Swineford however found the globulin fraction to be more potent. The proteins of low molecular weight (protamine histone nucleoproteids etc.) and the amino acids are inactive in this respect. This according to Doerr explains why bacteria—which are generally composed of such protein molecules—have relatively weak antigenicity.

In his recent work on immuno catalysis Sevag⁴⁵ has advanced the concept that antigens act as biocatalysts inasmuch as one molecule of an antigen induces the formation of many molecules of antibody while it forms no part of the reaction product (i.e. the antibody) and since the reaction is thermodynamically possible regardless of its presence. As a corollary it is held that since practically all proteins are antigenic all proteins are endowed with catalytic activity. According to this view the bacterial enzymes are the bacterial toxins.

It is to be noted that many proteins are active chiefly or exclusively in the native (or raw) state others only when cooked. The antigenicity of protein substances can be weakened or rendered inactive by the effect of heat digestive enzymes alkalis or acids. This explains the diminution of antigenic properties in heated milk boiled eggs etc. As Ratner and Gruehl have demonstrated in animal experiments this effect is probably attributable to coagulation of the proteins. On the other hand Rosenau and Anderson as well as Rapaport showed that proteins may be exposed to dry heat at a temperature of 140 C for two hours without destroying their antigenicity as determined by skin tests.

It is true that in the majority of cases the antigen is a protein. But as van Leeuwen P.

Schmidt and others have emphasized the nitrogen content of the allergically active substance is not a measure of the amount of the causative allergen present (see p. 543).

No decisive answer has as yet been given to the question as to whether complete antigens must be in principle of proteinogenous nature and whether therefore carbohydrates and lipoids can have more than a partial antigenic function. However authorities such as Zinsser, Enders and Fothergill⁴⁶ are of the opinion that the category of complete antigens includes not only proteins but also certain carbohydrates and carbohydrate lipid complexes. These authors maintain that such polysaccharides are themselves the antigenic agent and are not dependent for their effects upon any minute residuum of protein that may remain from the chemical processes employed in their purification.

Thus Bloch and Karrer were able to demonstrate that primin (the allergic principle of primrose) is a protein free substance of the lactone group. According to Touton the sensitizing agents of very many plants consist of unsaturated acid resins. That polysaccharides are the cause of certain bacterial and mold allergies was demonstrated by experiments in which guinea pigs were actively and passively allergized (Kesten and Mott). Moreover Feinberg and Watrous⁴⁷ showed that such simple chemicals of low molecular weight as chloramine T and halazone are capable of causing typical asthma and rhinopathy in exposed workers.

Absolute proof as to whether an allergen is operative by means of its protein content is quite often difficult to obtain for the following reasons. Allergens can be active in such incredibly high dilutions that the allergenic solution does not give a protein reaction on chemical analysis although it will produce a strongly positive biologic reaction. Thus Urbach and Fasal⁴⁸ demonstrated that none of the usual chemical tests can detect protein in a dilution of 1:100,000 but positive skin reactions can readily be produced with dilutions as high as 1:1,000,000,000. By means of the complement fixation technic Bosch, Gyorgy and

⁴⁵ FEINBERG S. M. and WATROUS R. M. *J. Allergy* 16: 209, 194.

⁴⁶ URBACH E. and FASAL P. *Arch. f. Dermat. u. Syph.* 164: 133, 1931.

Witebsky⁴⁶⁴ showed that dialysates of egg white that appeared chemically to be completely protein-free, but with which Prausnitz-Kuestner reactions were easily elicited, represented an antigen dilution of 1:10,000,000. Rimpau showed that the present dialysis membranes readily allow the passage of traces of protein. The diameter of an albumin molecule is only 5m μ .

These investigations have been discussed in some detail in order to bring out the important point that biologic methods are superior in this respect to the ordinary chemical tests. The fact that under the circumstances described the ordinary chemical methods will fail to demonstrate protein in the solutions, does not permit the conclusion, as drawn by W. Jadassohn,⁴⁶⁵ and by Grove and Coca,⁴⁶⁶ that the allergenic substance is not a protein nor a protein derivative of high molecular weight.

Details of the chemical structure of allergens are not known. It may safely be assumed, however, that the chemical composition varies considerably in different antigens. Occasionally, of course, the chemical difference between the allergens is only apparent, because they may contain a common chemical group. Thus, Bloch demonstrated that in a majority of cases of iodoform hypersensitiveness the patients react to the radical CH₃, and therefore, also to iodine-free compounds if they contain this radical. Furthermore, R. L. Mayer showed that skin hypersensitiveness to ursoil and to azo dyes is dependent upon a common factor, namely, formation of a body of quinone structure within the organism. Indeed, attempts have even been made to establish a so-called "common allergenic nucleus"—to be found in the greatest variety of substances—for the purpose of explaining their antigenicity (Wells, Duke). For obvious reasons these attempts have not been successful, nor does it appear likely that they ever will be. Another possible explanation has been suggested by the observation that numerous antigens contain both species-specific and group-specific allergens. According to Tuft, horse dander contains a horse aller-

gen (species-specific) that is also present in horse serum, and in addition a dander-specific fraction that is found only in horse dander. Eggs, regardless of their species (hen, duck, goose, pigeon, turtle), contain a common allergen and, in addition, species-specific allergens. F. A. Simon reported that mammalian serums contain not only their well-known species-specific components, but also an allergen in common. Certain organs or organ extracts (e.g., lens, liver, kidney, brain, testes) are distinguished by organ-specific as well as by species-specific allergens.

Klewitz and Wigand's⁴⁶⁷ investigations into the chemical behavior of allergens led them to the following conclusions—which, in the writers' opinion, however, cannot be applied to all allergens.

(1) Allergens are thermostable. Their biologic effectiveness is not altered by boiling for several minutes. The filtrate is just as active biologically as is the original extract.

(2) Allergens are dialyzable. The dialysate is as effective as the original extract.

(3) Allergens are quantitatively absorbed by animal charcoal. After treatment with carbon the extract is biologically inactive.

(4) Allergens are soluble in physiologic salt solution, but not in alcohol, chloroform, ether, or acetone. [In the present writers' opinion, this is true only of protein allergens and not, for example, of the allergenic principle of sage, which is soluble in petroleum ether.]

(5) Allergens are biuret-negative substances.

(6) Allergen extracts can be biologically active even when they contain no nitrogen [or, more cautiously and accurately stated, when nitrogen is not demonstrable by present chemical methods].

C. CHEMISTRY OF ANTIBODIES

It is now generally accepted that antibodies are modified serum globulins. As a result of recent investigations, antibodies are considered as large compact molecules composed of shells of peptide chains. They differ from normal globulins of the same animal largely in their greater molecular size.

According to Sabin's⁴⁶⁸ ingenious experiments with "marked antigens" (such as an

⁴⁶⁴ BOSCH, E., GÖRGY, P., and WITEBSKY, E. *Klin. Wchnschr.* 10, 2264, 1931.

⁴⁶⁵ JADASSOHN, W. *Schweiz. med. Wchnschr.* 56: 667, 1929. *Idem* and SCHAAF, F.; *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 79, 107, 1933.

⁴⁶⁶ GROVE, E. F., and COCA, A. F. *J. Immunol.* 10, 471, 1925.

⁴⁶⁷ KLEWITZ, F., and WIGAND, R. *Klin. Wchnschr.* 6, 1432, 1927.

⁴⁶⁸ SABIN, F. R. *J. Exper. Med.* 70, 67, 1939.

alum precipitated dye protein) antibody globulin represents the synthesis of a new kind of protein under the influence of an antigen

By means of the Tiselius electrophoresis apparatus Newell and his associates⁶⁹ fractionated human allergic serum into the albumin and the alpha beta and gamma globulins. Passive transfer tests revealed that the skin sensitizing antibody was present in the gamma globulin fraction. The antibody to ragweed in rabbits was also found in the same fraction. Practically all investigators are now in agreement that antibodies including the immune bodies for bacterial and virus infection are contained in this fraction. Thus Pauling and Campbell⁷⁰ showed that specific antibody can be formed *in vitro* by the denaturation and renaturation of gamma globulin in the presence of the antigen. By means of quantitative microanalytic chemical methods Heidelberger⁷¹ found it possible to measure the antibodies in serums in terms of specific nitrogen per unit volume. He achieved this by the removal of the non specific proteins after precipitation of the antibodies with a slight excess of antigen. The known nitrogen content of the antigen could then be subtracted from that of the precipitate. It was thus possible to show that the serum of rabbits which have undergone a long course of immunization may contain 7 to 10 mg of antibody nitrogen per cc. This means that one half to three fourths of the circulating globulin in the animal's blood is actually antibody protein. This is a figure that would have been thought impossible a few years ago.

Other characteristics of antibodies will be discussed in chapter X.

D BLOOD CHEMISTRY

There is extensive literature on the changes shown by the individual chemical components of the blood (cholesterol calcium phosphorus magnesium chlorides amino acids etc.) in the course of allergic diseases and in anaphylactic shock. These alterations appear to be so inconsistent that they must be designated as definitely noncharacteristic. But even when certain fluctuations in blood chemistry occur

the question still remains as to the extent to which these changes may represent the cause or the effects of an allergic process. The only regularly encountered alteration seems to be an increase in the potassium content of the blood. This was demonstrated in anaphylactic rabbits by Schittenhelm and in human asthma and hay fever by Kylin and Parker. Rusk, Weichselbaum and Somogyi⁷² found the potassium content of the blood in healthy human beings to average 19.5 mg per 100 cc. in urticaria 23.4 mg. in bronchial asthma during the asymptomatic period 23.6 mg. and in the acute asthmatic attack 24.4 mg. per 100 cc. Dees⁷³ likewise found serum potassium values in severe asthmatics higher than in normal subjects. However there was no significant alteration in the level after the subcutaneous injection of 0.75 cc. of 1:1000 epinephrine in either group even though the asthmatics obtained relief. The ability of urethane to produce relaxation of the bronchial muscles in cats appears to be related to an increase in the concentration of the potassium ion in the fluids of the respiratory tract (Boyd and Perry⁷⁴). On the other hand Bloom, Rusk and Kenamore, Parker and others have observed good therapeutic results from the use of large doses of potassium chloride in allergic cases. These results have however been strongly disputed by many others.

As clinicians pointed out long ago allergic manifestations in human beings are accompanied by marked disturbances in the water balance. Thus in asthma, migraine and urticaria water is retained and the fluid content of the blood decreases. Following these allergic attacks there is polyuria. Kern⁷⁵ correctly points out that increased intake of sodium tends to increase interstitial fluid and cause edema. This will favor the development of allergic reactions. On the other hand a decreased intake of sodium will increase the intracellular fluid and decrease interstitial fluid and edema. Thus salt restriction tends to inhibit allergic manifestations. The effects of hydration and of dehydration in allergic reactions are however strictly nonspecific.

⁶⁹ RUSK, H. A., WEICHSELBAUM, T. E. and SOMOGYI, M. J. A. M. A. 112: 392, 1939.

⁷² DEES, S. C. Ann. Allergy 3: 64, 1941.
BOYD, E. M. and PERRY, W. F. Proc. Soc. Exper. Biol. & Med. 57: 331, 1944.

⁷⁵ KERN, R. A. Am. J. M. Sc. 199: 778, 1940.

⁶⁹ NEWELL, J. M., STERLING, A., OXMA, M. F., BURDEN, S. S. and KREJCI, L. E. J. Allergy 10: 513, 1939.

⁷⁰ PAULING, L. and CAMPBELL, D. H. J. Exper. Med. 6: 211, 1942.

⁷¹ HEIDELBERGER, M. J. M. S. Na. Hosp. 9: 293, 1945.

Brief mention must be given to the claim that anaphylactic shock displaces the pH of the blood to the acid side (Mendéléeef, Zinz, and La Barré); before the appearance of shock, however, there is said to be a state of alkalosis. Tiefensee, as well as Diehl and Schenk, and others found that in asthma there was a shift of the blood reaction to the alkaline side, but that at the very height of the attack there was a tendency in the acid direction.

There appears to be an interesting and not yet fully understood relationship between diabetes mellitus and the allergic diseases: it is striking to note how infrequently these diseases occur simultaneously. In 1940, Joslin⁴⁷⁶ reported 30 asthma cases among 16,016 diabetics. Wilmer, Miller, and Beardwood found only 2 diabetics in a group of 4,762 allergy cases, while of 1,870 diabetic patients only 2 were definitely proved to be allergic. Swern found 6 diabetics among 4,000 asthma cases. Hajós had only 2 diabetics among 600 asthma patients. Kern reported 9 instances in which both conditions were present simultaneously, and concluded that although positive family and past histories of allergy and diabetes were quite frequently obtained from the same case, the two illnesses were rarely coincident. However, Joslin is of the opinion that these figures may be too low because of failure to question the patients carefully enough. He also states that hay fever is observed as an incidental finding in many diabetics.

Rost, and Barber and Oriel, as well as the writers, found that patients with neurodermatitis show an increased dextrose tolerance as revealed in the limited rise of the sugar curve following administration of glucose. According to Waldbott, Ascher, and Rosenzweig,⁴⁷⁷ there is an immediate but evanescent rise in blood sugar during allergic shock, followed by prolonged hypoglycemia.

E. URINARY PROTEOSES (ORIEL'S P SUBSTANCE)

The only demonstrable chemical alteration in the urine in allergies—and this point is still

highly controversial—consists in the appearance of the so-called P substance of Oriel. Barber and Oriel⁴⁷⁸ found that the urine of allergic individuals contained—particularly during attacks—a nitrogenous substance that could be extracted with ether. They called this the “proteose-like” or, by abbreviation, P substance. Its pathogenic importance and therapeutic value will be described later. From a strictly chemical point of view, it may be said that it is a polypeptide, composed of histidine, arginine, and lysine, and also containing nucleoprotein and glucosamine (Huellingstrung). Subsequent investigations have revealed that healthy, normal human beings eliminate such “proteoses.” However, persons suffering from allergic diseases excrete greater quantities—especially during allergic attacks. Boyd studied this substance chemically and concluded that it is a serum albumin contaminated with a mucoid. Tuft and Brodsky,⁴⁷⁹ from their own investigations and from a review of the literature, doubt that the P substance of Oriel has any specific immunologic basis.

For the extraction of the P substance, the modification of Thiers⁴⁸⁰ is recommended:

TECHNIC A quantity of 400 cc of urine preserved with chloroform (either a twenty-four hour specimen or the first urine passed after an attack) is acidified in reaction to Congo red paper with 25 per cent sulfuric acid, and thoroughly shaken with 200 cc of ether in a separatory funnel. After one or two hours of standing, there are formed an upper gelatinous and a lower liquid stratum. The lower stratum is discarded. The upper gelatinous layer is allowed to stand until the ether has completely evaporated. To the remaining liquid four times its volume of 95 per cent alcohol is added, and then sufficient concentrated sodium hydroxide until a color change is obtained in reaction to phenolphthalein. On filtration a white powder remains. This powder is washed three times with 95 per cent alcohol. After drying in an incubator, a portion of the powder is placed in sterile ampules.

A 1:1,000 dilution (0.01 Gm of the dry powder dissolved in 10 cc) is made with Evans' solution.

potassium biphosphate	3.63 Gm.
sodium biphosphate	14.318 Gm
sodium chloride	50.0 Gm
distilled water up to	1,000.0 cc

⁴⁷⁶ JOSLIN, E. P., ROOT, H. F., WHITE, P., and MARBLE, A. *The Treatment of Diabetes Mellitus*. Philadelphia: Lea, 1940.

⁴⁷⁷ WALDBOTT, G. L., ASCHER, M. S., and ROSENZWEIG, S. *J. Allergy* 10: 220, 1939.

⁴⁷⁸ BARBER, H. W., and ORIEL, G. *II*. *Lancet* 2, 1909, 1064, 1928; *ORIEL, G. II*. *ibid.* 2, 406, 1933.

⁴⁷⁹ TUFT, L., and BRODSKY, M. *J. Allergy* 4, 534, 1933.

⁴⁸⁰ THIERS, H. *Bull. Soc. franç. de dermat. et syph.* 46: 1233, 1933.

CHAPTER IX

ANTIGENS (ALLERGENS)

A GENERAL CONSIDERATIONS

AN ANTIGEN* is a chemical substance, a physical agent, or a living organism that stimulates the production of antibodies in the body and that, on encountering the antibodies, reacts with them in some observable manner.

We know in principle that every chemical, physical and bacterial agent can act as an antigen, nevertheless, a given substance or organism should not be considered as antigenic until the following criteria have been fulfilled (1) There must be proof of the existence of the allergen in the patient's environment (2) The clinical type of manifestation of the allergic reaction must be independent of the chemical and pharmacodynamic nature of the allergen likewise, the allergen extract employed in a skin test must be one to which there is an indifferent reaction in normal individuals (3) Removal of the allergen from the patient's environment must be followed by freedom from attacks (4) Contact with the allergen either by application, inhalation, ingestion or injection must elicit an attack, or at least there must be a positive skin reaction or a reaction of the shock tissue (5) The existence of a specific antibody to the antigen must be demonstrated by means of passive transfer of the hypersensitiveness or by specific desensitization of a skin site of a normal recipient prepared with the antibody containing serum of the patient

The most sensitive test for the identification of an antigen is the Schultz Dale method. However, its extreme specificity is in some respect a disadvantage in clinical work. As shown by Urbach and Wolfram,⁴⁸¹ the skepto phylactic technic is far more suitable for tests on man, while the anaphylactic experiment is recommended for tests on animals.

Since the number of antigens is incalculable, the guilty one can often be identified only after taking an exhaustive personal history of the patient, and often only after painstaking in-

spection of the patient's environment. The enormous difficulties that may arise in some cases will be discussed later in detail. Only a few salient and general points will be considered here. It must be especially emphasized that incredibly minute amounts of allergen often suffice to elicit severe symptoms. For example a patient of the present writers' reacted with severe anaphylactic manifestations when merely passing by a fish store. Another patient with dermatitis due to turpentine suffered a severe recurrence after merely standing for a moment near a freshly painted door. These illustrative cases will be far less of a strain on credulity when one recalls experiments showing that one millionth of a gram of a given allergen will evoke specific symptoms. Gruetz was able to provoke a definite local allergic reaction in a fish hypersensitive individual by the intracutaneous injection of 0.000,000,005 Gm. of protein derived from cooked fish. The senior writer was able to elicit positive skin reactions by the administration of 0.1 cc. of 1,000,000,000 solution of tuberculin, in cases of extreme hypersensitiveness to tuberculin.

An additional difficulty is due to the fact that the causative substance is frequently hidden or disguised. Who would be likely to suspect for example that red ice cream or pink tooth paste contained traces of phenolphthalein? Yet this chemical may be responsible for the manifestations in a specifically hypersensitive case. Or who would suppose that eating honey would bring on severe hay fever manifestations in an individual allergic to linden blossoms? The reason in this case was that the honey was gathered by the bees from linden blossoms.

The search for the causative allergen, especially in food allergies, is often made complicated and baffling by the fact that symptoms make their appearance only after ingestion of certain combinations or only if the food has been prepared in a certain manner (see p. 298).

A point that often seems to be neglected is the importance of the quantity of the allergens

* Synonyms: allergen, atopen, anaphylactogen.

⁴⁸¹ URBACH, E. and WOLFRAM, S. *Klin. Wchnschr.* 19: 1524, 1936.

These factors may, indeed, seem to contradict the very concept of hypersensitiveness, which is based essentially upon qualitative and not quantitative considerations. There are enough examples, however, of cases in which small quantities of allergen were tolerated but in which larger quantities elicited symptoms. This is particularly observed in food allergy: traces of egg may safely be taken by some hypersensitive patients, while a dram of egg will be followed by definite manifestations. The senior author reported the case of a patient who tolerated 10 cc. of milk but responded with severe urticaria to 750 cc. A similar situation occurs when one or two servings of a given food do not produce symptoms, while repeated helpings are followed by allergic reactions.

The *ricality* of antigens must be mentioned here. This refers to the reciprocal influence of two antigens simultaneously active in the organism. The result may be that the anaphylactic state is either inhibited or intensified, depending upon the existing quantitative and qualitative properties of the antigenic mixtures. Thus, Burky and his associates^{42, 43} have shown that rabbit lens protein complex can be rendered antigenic by simple fractionation. The alpha fraction causes high-titer precipitin production in rabbits. While both the beta and the gamma fractions are themselves antigenically inactive, each has the property of suppressing production of antibodies to alpha proteins. The pertinent question has been raised⁴⁴ as to whether the crystalline lens develops a protective mechanism based on specific inhibins, and whether these inhibins prevent the production of precipitins that, in turn, lead to degenerative changes in the eye. In the development of this idea it has been asked whether it is not possible that every endocrine organ produces such antigenic inhibins (see discussion of antihormones, p. 133).

As will be explained in greater detail below, it is very commonly not the food or drug itself that constitutes the allergen, but intermediary products and derivatives of the ingestants that are responsible for the reactions; these are

called secondary antigens (p. 115). Due consideration has not as yet been given to the importance of the so-called endogenous allergens: i.e., the substances of the body itself that for various reasons have become foreign to the body and have thus acquired antigenicity (p. 118).

The antigenicity of each substance is dependent on factors that are still not properly understood. However, Landsteiner⁴⁵ was able to show that the capacity of certain substances to produce eczematous contact type hypersensitiveness appears to be related to the lability of their Cl or NO₂ groups. Haurowitz and his co-workers⁴⁶ proved that the species specificity of natural proteins is attributable not to a single "determinant chemical group" but rather to a definite structural arrangement of tyrosine groups, free amino groups, and perhaps other groups on the surface of the protein molecule. By the introduction of chemical substituents such as acid and basic azo groups, and iodine and acetyl groups, into the molecule of native serum pseudoglobulin, they inhibited the specific precipitation of the serum pseudoglobulin by its homologous antiserum, thus indicating the destruction of species specificity by these procedures. Furthermore, there are certain substances that possess a special antigenic function even under ordinary conditions. According to J. Jadassohn, it would be possible to classify substances in the order of their antigenicity, beginning with those that allergize almost every human being, down to those that allergize only very rarely, if ever. Poison ivy, for example, allergizes approximately 60 to 65 per cent of all persons who come into contact with it (Spain and Cooke). Nickel dermatitis develops sooner or later in all persons who continue working at nickel plating (Schittenhelm and Stockinger). Nirvanol brings on exanthems in almost every child (De Rudder). Asthma afflicts almost everyone who works for some time under conditions exposing him to the inhalation of dust from grain infested by *Pediculoides ventricosus* (Frugoni and Ancona). On the other hand, the frequency of urticarial asthma in fur dyers is estimated by Curschmann to be about 10 per cent. The incidence of allergic manifestations due to quinine among

⁴² BURKY, E. L., and WOODS, A. C. *Arch. Ophthalm.* 57: 41, 1928.

⁴³ WOODS, A. C., BURKY, E. L., and WOODHALL, M. B. *Tr. Am. Ophthalm. Soc.* 29: 168, 1931.

⁴⁴ Editorial, *J. A. M. A.* 110: 1114, 1933.

⁴⁵ HAURWITZ, J., SARAFIAN, K., and SCHWERT, P. *J. Immunol.* 40: 391, 1941.

workers in quinine factories is estimated to be about 2 per cent (Dold). The antigenicity of these substances can be greatly changed, however, when the exposures do not take place under the usual occupational but rather under experimental conditions. It is then possible, as has been shown on page 41, to achieve up to 100 per cent allergization, even with the use of substances that ordinarily are only moderately antigenic by nature.

are injected intracutaneously with orchard grass pollen extract giving rise to a positive reaction. Up to this point the technique is the same as that of passive transfer (see p 146). However the same injections are repeated daily in exactly the same location until a reaction is no longer evoked that is the site is exhausted or more precisely the passively supplied antibodies are used up. The following day timothy pollen extract is injected into one of these sites (A) and into an unsensitized control site (C). Ragweed pollen extract is similarly injected into the sites B and D and the positive reaction in both shows that it is antigenically unre-

TABLE 15—Scheme of Exhaustion Test

Sites	Prepared with	Days after Initial Serum Injection					
		2	3	4	5	6	7
A	patient's serum	OG ++++	OG +++	OG ++	OG +	OG 0	T 0
B	patient's serum	OG ++++	OG +++	OG ++	OG +	OG 0	R ++++
C	patient's serum						T ++++
D	patient's serum						R ++++
E	unprepared						T 0
F	unprepared						R 0

OG = orchard grass pollen extract T = timothy pollen extract R = ragweed pollen extract

B THE BIOLOGIC IDENTIFICATION OF ANTIGENS

1 EXHAUSTION TESTS

In order to demonstrate whether two or more substances are allergenically identical or contain a common antigenic element, Coca and Grove⁴⁸ developed the exhaustion or crossed reaction test. The basic principle involved is the desensitization of passively sensitized skin sites with one antigen, followed by cross tests with a second antigen.

TECHNIC The serum of a patient hypersensitive, for example to timothy, orchard grass and ragweed is injected intracutaneously in amounts of 0.1 cc. each into four sites in a normal recipient (see Table 15). Twenty-four or forty-eight hours later two of these sites (A, B)

lated to orchard grass. The failure of timothy to elicit a reaction (in site A) although it does so in the control (C) indicates that the orchard grass has desensitized in relation to timothy. If by the same method it can also be shown that the reverse is true that timothy will desensitize to orchard grass, it may be assumed that their allergens are identical. If the reverse cannot be demonstrated it would appear that there is an allergic factor common to both substances, and that there is also a separate factor in the one.

2 CROSS NEUTRALIZATION TEST

The cross neutralization test has the same purpose as the exhaustion test, but achieves it by a quantitative approach. Furthermore, while in the exhaustion test the neutralization of the serum antibodies occurs gradually and *in vivo* (in the skin), in the cross neutralization test it is carried out *in vitro* and takes place promptly.

⁴⁸ COCA A. F., and GROVE E. F. J. Immunol. 10: 415 1923.

TECHNIC. A fixed quantity of antibody-containing serum is mixed under sterile precautions with varying proportions of the antigens before being used for the skin preparation of the recipient, just as in the neutralization test (p. 149). A day or two later, a related antigen is injected in each skin site. For instance, if timothy pollen extract was employed in the skin preparing mixture, June grass pollen extract may be used for the second injection. From the reactions produced it is possible to determine whether or not cross neutralization has occurred, and to form a quantitative estimate of its degree.

C. CLASSIFICATION OF ALLERGENS

The term *allergen* is used to designate any agent, whether chemical or physical, capable of eliciting antibody formation and thus a state of altered reactivity (allergy). The term *antigen* is customarily employed to denote living agents and their products that are able to call forth the production of antibodies. It will be seen from these definitions that there is no fundamental difference between allergen and antigen as regards the antibody mechanism. The only distinction is that the former is a nonviable and the latter a living agent. However, the phrase "antigen-antibody reaction" is rather loosely applied to all types of allergens.

Allergens are divided into two main groups, the exogenous and the endogenous.

The *exogenous allergens* are understood to include not only substances that exert their influence from outside the organism by way of the skin or mucous membranes, but also those allergens that are ingested (foods and drugs) or injected. They are subdivided into three groups:

(1) *Primary exogenous allergens* are all those foreign substances that, in their unaltered state, are capable of inducing antibody production. (2) *Secondary exogenous allergens* are those foreign substances that do not per se act as allergens, but assume the character of allergens only after transformation within the body by digestion, coupling, oxidation, reduction, or other chemical or physical alteration. (3) *Exogenous partial allergens* or *exogenous haptens* are those foreign substances that alone are not able to elicit specific antibody production, but have the capacity of reacting with antibodies specific for them.

The term *endogenous allergens* is taken to designate, first, substances produced by the transformation of autogenous material within

the organism, by autolytic, inflammatory, degenerative, or other processes, as a result of which they lose their biochemical identity and acquire antigenicity; and second, bacteria, viruses, fungi, and parasites, in so far as they multiply within the organism and stimulate the production of antibodies.

There is some evidence suggesting that the endogenous allergens may also be subdivided into primary and secondary allergens as well as endogenous haptens.

D. EXOGENOUS ALLERGENS

1. PRIMARY EXOGENOUS ALLERGENS

It is not possible, as yet, to consider the primary exogenous allergens along any definite line, as chemically, biologically, etc. We shall, therefore, classify them according to the manner in which they exert their influence—viz., as inhalants, ingestants, contactants, physical agents, etc. Each of these types of allergens will receive detailed discussion in Part Two (inhalants, p. 236, contactants, p. 373, foods, p. 295; drugs, p. 316 and 335, bacteria, p. 435, parasites, p. 480, physical agents, p. 409).

2. SECONDARY EXOGENOUS ALLERGENS

This group comprises those substances reaching the organism from without that do not act as antigens, per se, but do so only after having been transformed by chemical alterations or by physical changes, such as digestion, oxidation, reduction, or coupling. In foods, especially, the allergen is frequently not the material as actually ingested, but a split product formed in the course of intermediary metabolism. This should be suspected in all instances in which skin tests are consistently negative. For example, the senior author was able to show that a food may become allergenic only when acted upon by the bacterial flora of a certain portion of the intestines. In one such case, in which ingestion of cow's milk regularly elicited urticaria after eight hours, colonic irrigation given at this time totally inhibited the urticarial response. The same result was achieved in other cases by changing the nature of the intestinal flora by means of *Bacillus acidophilus*.

Similar conditions seem to prevail in drug allergies, as evidenced by negative skin tests

with the allergen and by negative passive transfer. Employing the reversed Prausnitz-Kuestner method (see p 148), Kenedy⁴⁸⁷ was actually able to show that the drug itself was not the allergen, but rather products formed from it within the organism. He demonstrated this by administering phenolphthalein twice by mouth to a normal recipient. About four hours after the second dose, the subject received intracutaneous injections of serum from the allergic patient as well as control serum from a normal individual. A positive skin reaction after twenty-four hours, at the site of the injection of allergic serum, proved that this serum contained specific antibodies to phenolphthalein. The fact that there was no reaction when the allergic serum was injected first and then phenolphthalein (i.e., classic Prausnitz-Kuestner method), while the drug after resorption elicited definite local manifestations, gave strong support to the idea outlined above. Using the same method, Lang and Dér⁴⁸⁸ succeeded in transferring hypersensitiveness to quinine, iodine, and neoarsphenamine in animals—a result only very rarely achieved by means of the ordinary methods of passive transfer.

3 EXOGENOUS HAPTENS

Exogenous haptens are, in the words of the brilliant Landsteiner⁴⁸⁹ who discovered them, substances foreign to the body and in themselves not antigenic, but acquiring antigenicity on conjugation with an auxiliary proteinogeneous substance as the carrier. As a result of this union, "complete antigens" or conjugate protein antigens are formed. Haptens per se are unable to induce antibody formation. However, they can call forth specific reactions, either with the antibody *in vitro* or in living hypersensitive tissues. When sensitization has already been produced by the combined hapten-protein, the hapten alone may produce an allergic reaction—even in the absence of the combining protein (Landsteiner and van der Scheer). The specificity of the conjugated antigen is, to a great degree, independent of the nature of the protein, but is determined by the properties of the nonprotein portion or hapten (Avery and Goebel). The haptens are some-

times referred to as "partial" antigens because of their capacity to react with antibodies and their failure to stimulate production of the latter.

According to Landsteiner, the fact that only proteins, and not lipoids or carbohydrates are capable of acting directly as antigens is to be explained by the physical constitution of their components. Proteins, as is well known, are composed of large molecules. From this point of view it is interesting to recall the experiments in which haptens of various kinds were successfully complemented and transformed into complete antigens by conjunction with substances not antigenic at all but characterized by their large molecular surface and highly adsorptive nature (e.g., suspensions of colloidal or kaolin). Haptens may be simple chemicals or drugs, as well as complex compounds, such as lipoids or polysaccharides.

Long before the hapten theory was formulated, Obermayer and E. P. Pick (1903-1906) iodized proteins and thus obtained antigens that, when injected into animals, produced antibodies specific for the iodized antigen, but not for the original protein. On the basis of clinical observations, Wolff Eisner (1907) first emphasized the fact that medicaments introduced into the organism might form compounds with the body protein or serum protein, thus forming a new substance ("drug protein") possessing chemospecific antigenicity.

The question of whether sensitivity to certain drugs may result from a hapten-protein combination formed in the organism was answered by the very interesting experiments of Rosenthal.⁴⁸⁹ He showed that when rabbits were fed phenolphthalein or are given injections of colloidal phenolphthalein, their serum will contain an antigenic substance formed by the conjugation of phenolphthalein with autogenous protein. When rabbits receive repeated intracutaneous or intramuscular injections of this phenolphthalein conjugate, and then, after a certain lapse of time, are re-injected, positive skin reactions are seen. There were never any such reactions when phenolphthalein alone was used. Likewise, Aossima⁴⁹⁰ was unable to allergize guinea pigs

⁴⁸⁷ KENEDY D. *Gior ital dermat* 57 965 1934

⁴⁸⁸ LANG M and DER O. *Muenchen med Wchnschr* 74 59 1927

⁴⁸⁹ ROSENTHAL, S R. *J Immunol* 34 251, 1938

⁴⁹⁰ AOSSIMA, S. *Jap J Dermat* 48 2 1940

with antipyrine alone. However, he could achieve sensitization by adding such proteins as human or animal blood or serum, including guinea pig blood, to an antipyrine solution, and injecting the mixture intracutaneously. Moreover, Oriel⁴¹ succeeded in isolating from the urine of a patient with allergic edema due to acetylsalicylic acid an aspirin-proteose complex which elicited a positive skin test, while both the drug and the proteose alone failed to do so.

Within the past few years numerous authors—notably Landsteiner,^{59, 492} Sulzberger,¹⁶⁹ and Schwartz⁴⁹³—have shown that simple chemical compounds can be converted into conjugated antigens by being attached to proteins. Their experiments have been especially significant, since they showed that repeated irritation of the skins of human beings and animals by simple chemical compounds, such as certain chemicals, dyes, and drugs, can bring about states of hypersensitivity having the characteristics of contact dermatitis.

It is to be noted that allergization can be achieved only by epidermal or cutaneous contact with these chemicals, and not by means of intravenous administration. This fact seems to prove that the damaged cutaneous tissue furnishes the protein necessary to complement the potential haptens, such as the chemical or drug, and thus to produce complete antigens. This would help to explain the high incidence of allergic contact dermatitides.

The same mechanism also seems to be the basis for the "depot injection method" of Lehner and Rajka. These authors found that it was possible to achieve allergization with substances that are not, in themselves, antigenic by nature, provided they are injected daily or every other day into the same skin site. Others have achieved similar results by administering the non-antigenic substance along with the injection of smallpox vaccine, or along with local exposure to strong sunlight or to roentgen rays. Furthermore, Haxthausen²⁶⁷ demonstrated that when simple chemical compounds, such as mercury or

chromic salts, were mixed with foreign protein—for example, animal serum or monilia, staphylococci, or other organisms—a cutaneous hypersensitivity of eczematoid character could be produced. Tezner and Reiter achieved allergization of the human skin to homologous serum by employing smallpox vaccine or horse serum as carrier substances.

Not only foreign serum, however, but homologous serum as well, is capable of acting as the synergist. In this connection, the experiments of Klopstock and Selter⁴⁹⁴ are especially noteworthy, since they closely approximate natural conditions. These authors produced such a high degree of allergization in guinea pigs by administering diazotized atoxyl mixed with guinea pig serum that subsequent reinjection of the mixture caused anaphylactic death. Similarly, Samson, as well as Goetz, and Lehner and Rajka, and also others succeeded in rendering human beings sensitive to morphine and to atropine by preparatory injections of mixtures of autogenous serum and the drug. Guinea pigs have also been sensitized to aminopyrine by injections of autogenous serum mixed with aminopyrine. According to Jacobs, rabbits injected with iodized rabbit serum responded with the formation of precipitins: in other words, following linkage with the homologous protein of the animal, iodine became a complete antigen.

Another important type of partial antigen is represented by lipoids that become complete antigens when combined with an appropriate carrier substance. These lipid haptens are widespread in animals in the form of the *heterogenetic* antigens (Forssman⁴⁹⁵). When a rabbit receives an injection of aqueous extract of horse kidney, antibodies are formed that are directed not only against horse kidney, but also against sheep's blood. In other words, the rabbit serum acquires the property of hemolyzing sheep erythrocytes. Conversely, a hemolytic serum produced by injecting sheep erythrocytes, gives positive complement fixation reactions with horse kidney extract. Thus, sheep erythrocytes and horse kidney contain a common antigenic component, and

⁴¹ ORIEL, G. H. *Proc. Roy. Soc. Med.* 24: 1171, 1931.

⁴⁹² LANDSTEINER, K., and CHASE, M. W. *J. Exper. Med.* 66: 337, 1937.

⁴⁹³ SCHWARTZ, L., and HOCKER, C. D.: *Pub. Health Rep.* 51: 493, 1936.

⁴⁹⁴ KLOPSTOCK, A., and SELTER, G. E. *Klin. Wchnschr.* 6: 1662, 1927.

⁴⁹⁵ FORSSMAN, J. *The Heterogenetic Antigens*. *Handb. d. path. Mikrobiol.* (ed. 3), 3: 469, 1932.

this same component is demonstrable in the organs and red blood cells of numerous other animals. The Forssman antigen has hitherto always been regarded as a lipid, since it is soluble in alcohol. Recent investigations, however, would seem to indicate that it consists of a carbohydrate complex.

Numerous authors have been able to allergize animals with conjugated lipoids. Sachs, Witebsky, and others have shown that lipoids in the human organism are capable of producing autogenous antigens that play an important part in the pathology and serology of syphilis, as well as of other diseases.

The investigations of Heidelberger have called attention to the great importance of the carbohydrate haptens. Heidelberger's work would seem to indicate that these are responsible for the specificity of bacterial antigens.

The mechanism of haptization probably plays a much more important rôle than is now realized. It would seem to be responsible for the majority of allergic dermatitides and for drug allergies involving not only the skin but also the mucous membranes.

E ENDOGENOUS ALLERGENS

In contrast with *exogenous allergy*, the principal causal agents of which are inhalants, ingestants, injectants and contactants, the term *endogenous allergy* designates those hypersensitivities in which the allergens are formed within the body. The endogenous allergens may be divided according to their origin into two groups, the *auto endogenous* and the *hetero endogenous*. We speak of *auto endogenous* allergens when autogenous substances (e.g. body cells and their products, or tissue fluids) acquire antigenicity under certain conditions that will be discussed below. *Hetero endogenous* allergens are foreign substances, chiefly of proteinogenous nature, that enter the organism from without but call forth antibody formation only after multiplication or growth within the body. The chief types of hetero endogenous allergens are bacteria, viruses, fungi, and certain parasites, or their products.

For the sake of clarity, it is necessary at the outset to differentiate the endogenous allergens from those agents with which they might possibly be confused. Thus, ingestants (foods

or drugs) are often not allergenic per se but acquire antigenicity only after transformation by metabolic processes. The resulting substances, in view of their origin, are properly designated as secondary exogenous allergens. Likewise exogenous partial antigens (exogenous haptens) such as ingested or injected drugs, which become complete allergens only after conjugation with body protein, must also be thought of as essentially exogenous in nature. Finally, in the case of parasites both possibilities exist: they have to be considered as exogenous when acting as a result of inhalation (e.g. ascaris in laboratory workers), and as endogenous when the sensitization occurs after their growth or multiplication within the body.

It is interesting to note that authors in different fields of medicine as early as 1910 tried to explain certain diseases on the basis of allergy to the body's own protein. Terms such as 'auto anaphylaxis' (Elschnig⁴⁹⁵), "auto sensitization" (Whitfield⁴⁹⁷), endo allergy" (von Bergmann⁴⁹⁸), and 'intrinsic asthma' (Rackemann⁴⁹⁹) give some indication of this trend. However, in contrast to the multiplicity of clinical and experimental studies on exogenous allergy, only a very few investigators have worked on the problem of endogenous allergy. (Barber⁴⁹⁵ Berger,⁴⁹⁹ von Bergmann,⁴⁹⁸ Doerr,¹⁸ Duke,⁵⁰⁰ Elschnig,⁴⁹⁵ Lichtwitz,⁵⁰¹ Rackemann,⁴⁹⁹ Salen,⁵⁰² Sulzberger,⁴ Urbach,⁵⁰³ and Whitfield⁴⁹⁷). The evidence that rheumatic fever and allied diseases are due to an endogenous allergy to the products of proteolysis of the tissues as well as to metabolites of invading micro organisms was thoroughly considered by Lichtwitz⁵⁰⁴ in his recent monograph. Most of the authors mentioned, however, confined themselves to the rather

⁴⁹⁵ ELSCHNIG A. Arch. f. Ophth. 75: 459, 1910; 76: 509, 1910; 78: 519, 1911.

⁴⁹⁷ WHITFIELD A. Proc. Eighth Internat. Cong. Dermat. Copenhagen 1930, p. 142.

⁴⁹⁸ BERGMANN VON Funktuelle Pathologie. Berlin: Springer 1932.

⁴⁹⁹ BERGER W. Med. Klin. 34: 893, 989, 1938.

⁵⁰⁰ DUKE W. W. Asthma Hay Fever Urticaria and All. ed. Mani. Lectures on Allergy, ed. 2. St. Louis: Mosby 1936.

⁵⁰¹ LICHTWITZ I. Functional Pathology. New York: Grune & Stratton 1941.

⁵⁰² SALÉN E. B. Acta med. Scand. (suppl.) 494: 1934.

⁵⁰³ URBACH E. Klinik und Therapie der allergischen Krankheiten. Vienna: Maudrich 1935.

⁵⁰⁴ LICHTWITZ I. Pathology and Therapy of Rheumatic Fever. New York: Grune & Stratton 1944.

narrow limits of their specialties, such as the skin, the eye, the female sexual organs, and bacteria. Since no comprehensive survey existed, an attempt was made⁵⁰⁸ to present the theoretic foundation and clinical manifestations of the endogenously acquired hypersensitivities.

The concept of endogenous allergy is, as will be seen below, the logical supplement to that of exogenous allergy. It leads us to search not only for allergens coming from without but also for those arising within the body. This knowledge, in turn, has stimulated the development of new diagnostic methods for identifying endogenous allergens, which for obvious reasons cannot be demonstrated by the same technics as those used for the exogenous. And, above all, this concept has been instrumental in attempts to work out methods of treatment.

1. AUTO-ENDOGENOUS ALLERGENS

Auto-endogenous allergens, or, by condensation, auto-allergens, may arise from many different sources. We shall exclude from consideration those that are physiologic, so to speak, because they do not elicit any morbid reactions. An example would be the type responsible for the formation of the blood group antibodies. The pathologic auto-allergens, on the other hand, consist of altered autogenous proteins that—as a result of autolytic, inflammatory, degenerative, or other physicochemical processes—have become foreign to the organism and have thus acquired antigenicity. More specifically, auto-allergens are derived from the breakdown or catabolic products of diseased organs, particularly the skin, endocrine glands, and liver, from intermediary or split metabolic products, and finally from the disintegration of tissue fluids (exudates and transudates) and hemorrhages.

Autogenous allergens may be subdivided, as are the exogenous allergens, into primary and secondary forms, and possibly also into haptens.

Primary allergens are those that originate directly from diseased tissues or abnormal endocrine products. As an example of how a diseased organ may give rise to autogenous allergy, one may cite sympathetic ophthalmia

It has been established by immunologic methods (see below) that this condition represents an allergic response to the patient's own uveal pigment. In addition, there is evidence that abnormal endocrine products may cause allergic manifestations, as demonstrated serologically by antihormones.

Secondary auto-endogenous allergens are conceivably formed in the following manner. When a tissue is sensitized, whether by exogenous or by endogenous allergens, and its protein as a result of a severe reaction is rendered foreign to the organism, this altered protein may act as a new allergen on other organs. This is demonstrated clinically by the appearance of a different type of manifestation in a different organ after a suitable latent period. The following case may clarify this concept.

A woman 21 years of age and in good health, who had never previously received any type of serum, was given a prophylactic injection of diphtheria toxin-antitoxin. Forty-eight hours later the site of injection (the upper part of the thigh) presented a severe local reaction with diffuse and brawny swelling (Arthus phenomenon). This persisted for six days and was followed by pains in several joints. On the tenth day after the injection an urticarial exanthem appeared on the posterior aspects of the arms and there was also a simultaneous flare-up of the reaction in the site of injection. Nine days later the urticarial outbreak increased in intensity and spread to the face, neck, back, and lower extremities. Four days later the urticaria was replaced by an acute vesicular dermatitis (Fig 27), although no local therapy had been used.

In view of the fact that the second urticarial rash occurred just nine days after the first one, it may properly be classified as a fractionated serum sickness. The eczematous rash, however, we consider to be an expression of an allergy to a secondary endogenous allergen. The latter arose from the "heterogenization"^{*} of cutaneous proteins as a result of the severe local anaphylaxis (Arthus phenomenon). This conclusion is further supported by the fact that eczematous lesions have never been observed in serum sickness, since the shock structures are the blood vessels and not the epidermis. Hence the dermatitis may best be explained on the basis of an endogenous allergy caused by a secondary endogenous allergen. To analyze this case further it is apparent that the horse serum in the antitoxin was a primary exogenous allergen, producing the fractionated serum sickness. It was not the horse serum, however, but the body proteins altered by the severe Arthus phenomenon that presumably allergized the epidermis, producing a dermatitis.

* By heterogenization is meant such alteration of body protein that it becomes foreign (heterogenous) to the organism.

The concept of an endogenous allergy caused by secondary endogenous allergens was first formulated on an experimental basis by Manwaring and his associates and clinically by Barber. The latter assumed that certain bacteria by acting on a previously allergized organ such as the liver so alter some of the liver protein that it becomes allergenic and must be considered a secondary endogenous

capacity of reacting specifically with appropriate antibodies but lack the ability to call forth the production of antibodies. We should like to advance the hypothesis that endogenous lipoids and carbohydrates as well as endogenously formed porphyrin may under certain circumstances act in this way. This view would be analogous to the well known fact that lipoids and carbohydrates when introduced



FIG. 27 VESICULAR DERMATITIS AS EXPRESSION OF ALLERGY TO SECONDARY ENDOGENOUS ALLERGEN
Complicated mechanism underlying this is indicated in text

allergen. Barber stated it as his belief that the appearance of urinary proteoses in such cases was evidence of the presence of a secondary endogenous allergen. He tried to explain on the basis of this mechanism the clinical observation that different allergens may elicit the same allergic symptoms in one person.

In addition to the primary and secondary endogenous allergens it is conceivable that diseased or altered tissue substances may assume the character of *haptens*. This means that the autogenous substances acquire the

into the body may act as exogenous haptens and become complete antigens on conjugation with proteins. The same concept may apply even more to hetero endogenous allergy with particular reference to bacteria. On the basis of the investigations of Heidelberger and Avery and of others it seems likely that it is the carbohydrate and lipid constituents rather than the proteins of bacteria that are responsible for allergization. Sensitization to autogenous lipoids has been demonstrated by Henning.

In this connection mention should be made of the highly significant work of Burky⁵⁶. His investigations serve to explain the allergic manifestations observed in infectious diseases, and also help clarify the mechanism of physical allergy. Burky showed that staphylococcus toxin prepared in a broth made from rat muscle allergizes rats to this broth, and these animals also become hypersensitive to trauma, probably because it releases into the blood substances identical with those contained in the broth. Comparable observations were made by others with homologous skin autolysates in rabbits, since sensitization was produced only if increasing doses of Staphylococcus toxin were administered simultaneously (see below). Applying the Burky technic, Schwentker and Comploier⁵⁶ found that most persons suffering from scarlet fever developed circulating antibodies to their own kidney tissues. This led the authors to conclude that streptococcus toxin damages some of the kidney tissue during the primary stages of scarlet fever—even though the damage may be clinically undetectable. The denatured kidney proteins combine with the bacteria and/or their products and are thus rendered antigenic. Hence, the production of specific antibodies may be assumed to be the cause of postscarlatinal nephritis.

Karady's⁵⁷ experiments indicating that the organism's own protein can be so changed by various physical agents (e. g., heat and cold) as to acquire antigenicity, are more fully discussed on p. 135.

We fully appreciate the fact that the concept of endogenous allergy, attractive as it may be on clinical grounds, must remain hypothetical as long as the endogenous allergens cannot be isolated in order to demonstrate an antigen-antibody reaction. It will be readily understood that the antibodies produced by these auto-allergens cannot be demonstrated by the usual methods. Occasionally it is possible to find the endogenous allergen in the patient's urine in the form of Oriol's P substance. Rarely, the antigen is to be found in the blood, as for example in certain menstrual allergies

(Géber, Urbach), in the menstrual discharge (Salén), or in the milk (Duke).

If, however, future experimental work should confirm the idea of an endogenous allergy due to secondary as well as primary endogenous allergens and haptens, it would serve to explain a host of hitherto vague symptoms that possess some of the characteristics of hypersensitivity but have never been shown to be due to exogenous allergens.

2. CLINICAL MANIFESTATIONS OF AUTO-ENDOGENOUS ALLERGY

The clinical manifestations of auto-endogenous allergy will be described here under headings that group the substances to which they are due, as follows.

a) BLOOD AND BLOOD SERUM AS AUTO-ENDOGENOUS ALLERGENS

The classic proof of the existence of auto-allergens—and incidentally, the most thoroughly investigated example in this connection—is *paroxysmal hemoglobinuria*. This term describes the clinical syndrome in which, after exposure to cold, there appear chill, fever, and a transitory hemoglobinuria, accompanied by manifestations of the nature of Widal's hemoclastic crisis (drop in blood pressure and leucocyte count, change in refractometric index of the serum, change in coagulability of the blood, etc.). Donath and Landsteiner⁵⁸ have shown that a true antigen-antibody reaction is the cause of these manifestations and that antibodies (autohemolysins) directed against the body's erythrocytes have been produced within the organism. Miyakawa experimentally demonstrated the appearance of antibodies following the destruction of erythrocytes in the blood stream by means of phenylhydrazine.

Autohemagglutination is the clumping of erythrocytes into irregular masses, visible to the naked eye as well as microscopically, by the action of the individual's own serum, without bacterial action, at room temperature and reversible at body temperature. It is known to be due to the interaction of the agglutinin of the serum with the agglutinin of the

⁵⁶ SCHWENTKER, F. F., and COMPTON, F. C. - J. Exper. Med. 70: 123, 1939.

⁵⁷ KARADY, S. - J. Immunol. 37: 457, 1939.

⁵⁸ DONATH, J., and LANDSTEINER, K. - Ztschr. f. klin. Med. 58: 173, 1903.

erythrocytes Since this union occurs only at temperatures below that of the body (and in the laboratory at refrigerator temperatures) the antigen is known as cold hemagglutinin.* A rise in the auto agglutination titer is observed in diverse pathologic states including virus pneumonia acute and chronic acquired hemolytic anemias leucemia lymphoblastoma acute bacterial infections cirrhosis of the liver syphilis trypanosomiasis malaria carcinoma relapsing fever infectious mononucleosis epilepsy bland venous thrombosis snake bite poisoning Raynaud's syndrome and hemolytic reactions from sulfonamides When the cold agglutinin titer is sufficiently high clinical symptoms may sometimes appear after exposure to cold It should be noted that the isoagglutinin is active not only against the patient's own erythrocytes but against all types of human red blood cells as well as to some extent against those of other animal species (Dameshek³⁰⁹ Turner and Jackson³¹⁰) Hence it may be related to the heterogenetic (Forssman) antigen

As regards the mechanism of its formation Dameshek³⁰⁹ considers the effect of the infection itself—as well as the possibility that a sufficient number of red cells may be so altered by a sulfonamide compound as to serve as an antigen with the subsequent formation of an agglutinating antibody—a clear instance of endogenous allergy The titer of cold agglutinins rises in atypical pneumonia during the second week after the onset of respiratory symptoms (Turner and Jackson³¹⁰) and is therefore a diagnostic aid Confusion in the typing and cross matching of blood may arise because of the presence of this antibody but may be avoided by special laboratory precautions (Lindsey³¹¹) In a very severe case of autohemagglutination Nickum³¹² effected a cure by means of transfusions of citrated blood and intravenous injections of 10 cc. of heparin in 10 per cent glucose and saline An excellent review article on cold hemagglutination was published by Stats and Wasserman³¹³

Recent investigations concerning the Rh factor clarify the mechanism of one of the most interesting forms of endogenous allergization This antigen—named for the fact that it occurs in the erythrocytes of the *Macacus rhesus* monkey—is contained in the red blood cells of about 86 per cent of human beings and may give rise to isoimmunization under certain circumstances An Rh negative woman gravid with an Rh positive fetus (the characteristic being inherited as a mendelian dominant) will form anti Rh antibodies (agglutinins) as a result of the passage of fetal erythrocytes through the normal or diseased placenta into her circulation Thus she is actively sensitized to an endogenous allergen (fetal Rh factor) and will thereafter react to transfusions of Rh positive blood with hemolysis agglutination and the consequences thereof At the same time the specific antibodies reach the fetal circulation since the placenta is permeable to them and as a result the fetus is passively sensitized so to speak to its own erythrocytes—or more specifically to an antigen contained in its erythrocytes This fetal antigen antibody response is responsible for intravascular hemolysis setting up a sequence of pathologic changes culminating in erythroblastosis (p. 366)

Whitfield drew attention to the fact that deep seated *ecchymosis* due to trauma fractures or torn muscles was followed within nine to twelve days by generalized erythematous urticarial eruptions Similar observations have been made by Barber Urbach and others Particularly interesting is the occasional occurrence of urticarial zones surrounding hemorrhagic purpuric lesions as noted by Whitfield presumably these are due to a local auto allergic mechanism

It must be noted however that human beings and animals can become hypersensitive not only to the erythrocytes of their own blood but also to their own serum or plasma Bizzozzeri has demonstrated that repeated intracutaneous injections of their own serum sensitized the skin of 9 of 25 persons on whom the experiment was performed Comparable to this are the reports of Nelli Netter Nathan and Grundmann Marie and Tezner and Reiter who have described the appearance of serum sickness following injections of homologous serum in individuals who had previously

* Synonym cold agglutins autoagglutinin paragneuromas

³⁰⁹ DAMESHEK W. J. A. M. A. 123 77 1933

³¹⁰ TURNER J. C. and JACKSON E. B. B. t. J. Exptl. Path. 24 17 1933

³¹¹ LINDSEY D. New Orleans M. & S. J. 95 3 17 1943

³¹² NICKUM J. S. Connecticut U. Sta. M. J. 475 1943

³¹³ STATS D. and WASSERMAN L. R. Med. ne 22 363 1943

received human serum Marks⁴⁴ observed the sensitization of two patients from repeated subcutaneous injections of their own serum given in the treatment of lymphopathia venereum. Schmidt even reported a case of death in protracted shock following a second subcutaneous injection of measles convalescent serum eight days after the first.

Eickhoff, as well as Geissendoerfer, duplicated these observations in animals. Autogenous serum repeatedly administered parenterally was capable of eliciting allergic reactions almost identical with those elicited by foreign serums.

b) EXUDATES AND TRANSUDATES AS AUTO-ENDOGENOUS ALLERGENS

This grouping comprises cases of endogenous allergy due to absorption of autogenous protein contained in transudates and exudates that has become, in effect, foreign to the body. Duke,⁴⁵⁰ 515 for example, published a report of 3 women who had a serum-sickness-like symptom complex following rapid absorption of their own milk. In each case the condition could be relieved through the use of the breast pump. In one instance, in which the condition followed the weaning of a baby, the symptoms were so severe that it was necessary to administer epinephrine repeatedly. In one of the patients who had been secreting about 1 dram of milk a day during the seven years following the weaning of her child, passive transfer was successful only by means of her own milk, but not of cow's milk. Furthermore, injection of 0.02 cc. of a 1:10,000 solution of her own milk was followed not only by a most severe urticarial reaction but also by an attack of asthma and an intense general pruritus. Subsequent to these reactions, the patient became insensitive to her own milk and the secretion of milk decreased, stopping altogether after about three weeks.

Falls, Freda, and Cohen⁵¹⁶ found that a large percentage of nonpregnant women in the child-bearing ages give a positive immediate reaction to the intracutaneous administration of 0.01 cc. of colostrum, while most pregnant women do not. The authors conclude that the body

is allergized to the protein by the small amount of colostrum produced in the breasts of non-pregnant women after puberty. Pregnancy, by gradually increasing the colostrum production, creates a temporary specific anergy to this protein. Even though this reaction is not sufficiently reliable to constitute a practical test for pregnancy (Weisman and Snyder⁵¹⁷), it nonetheless reveals a striking incidence, involving about 75 per cent of women of child-bearing age, of a common form of endogenous allergy. However, Davey and Daley⁵¹⁸ found the test to show an almost complete lack of specificity. A similar mechanism of specific anergy in gravid women, resulting in a cutaneous insensitiveness to fetal protein, will be discussed in the section on allergy to pregnancy.

Rapid absorption of pleural or peritoneal exudates, or of synovial effusions following aspiration of a joint, has occasionally been observed to bring on serum-sickness-like conditions (such as urticaria, angioneurotic edema, hydrarthrosis, and fever). In a case observed by one of us, angioneurotic edema occurred following each refilling of a therapeutic pneumothorax. In this connection, mention should also be made of the urticarias following vaccination, burns, and prolonged exposure to sunlight. We might also include here the allergic reactions that have been observed following injections of autogenous exudates.

c) PROTEOSES EXCRETED IN THE URINE (ORIEL'S P SUBSTANCE)

There is an extensive literature on the question as to whether the proteoses found by Barber and Oriel⁴⁷⁸ in the urine in allergic diseases are specific endogenous allergens. Here we should like to consider only the following questions: Is this substance excreted in greater quantity during allergic attacks? Is it specific? Does it have any therapeutic value?

None of these queries has as yet have been satisfactorily answered, despite the fact that numerous investigations have been made in the past twelve years. Many authors, including Tuft and Brodsky, Villalba, and Urbach, have confirmed the finding that larger amounts

⁴⁴ MARKS, M. M. South M. J. 35: 1097, 1942.

⁴⁵⁰ DUKE, W. W. J. A. M. A. 95: 1447, 1937.

⁵¹⁶ FALLS, F. H., FREDA, V. C., and COHEN, H. H. Tr. Sect. Obst., Gynec. & Abdom. Surg., A. M. A. 53: 62, 1940.

⁵¹⁷ WEISMAN, A. I., and SNYDER, A. F. Am. J. Obst. & Gynec. 41: 431, 1941.

⁵¹⁸ DAVEY, J. F., and DALEY, D. E. Canad. M. A. J. 52: 371, 1945.

of P substance are excreted during allergic attacks than in the free intervals. The specificity of the proteoses however is emphatically disputed by Freeman, Cormia, Cornbleet and many others while Burgess⁵⁹ who checked Onel's observations at the request of the British Medical Association as well as van Leeuwen, R. Barany, Kallos, Black, Shelmire and Gate confirmed Onel's findings. Gate⁵⁰ reported the interesting observation that the P substance produces specific reactions only when injected together with the serum of the same individual. Regarding

be excreted in the urine in such a state that they can be utilized for testing or therapy. In cases of exogenous allergy however the allergens generally will have been so altered or destroyed that their derivatives in the urine will have lost their antigenicity.

Furthermore we believe that the technic of Thiers⁴⁸⁰ should always be employed for the extraction of the proteoses. Together with Gate we should like to warn against the use of strong concentrations for test purposes such concentrations may act nonspecifically and may occasionally elicit severe focal and general reactions. We recommend that the first injection should not exceed a concentration of 1:10,000. We are of the opinion that in cases of endogenous allergy therapeutic trial with autogenous urinary proteoses is warranted. FIGURE 28 shows an angioneurotic edema of unknown origin. This condition could be evoked by administering autogenous urinary proteoses. After ten injections the patient became asymptomatic apparently as a result of the treatment. A similar mechanism may perhaps be the basis of the good results obtained with auto urotherapy by Jauson and Pages in light dermatoses by Jauson and Paleologue in chronic dermatitides by Aujaleu and Colombes in a severe case of angioneurotic edema and by Skrokowska in a case of erythema annulare resistant to other treatment.

d) DISEASED TISSUES AS AUTO ENDOGENOUS ALLERGENS

While only relatively few observations can be cited to illustrate the action of altered tissue proteins as endogenous allergens, it is our conviction that this mechanism is operative far more often than can be actually demonstrated in the present state of knowledge.

(1) Altered Tissues of the Eye as Endogenous Allergens

Long before the term endogenous allergy was coined certain diseases of the eye were considered as clinical expressions of autoanaphylaxis. As early as 1910 Elschnig¹⁰⁶ assumed that the cause of sympathetic ophthalmia was a sensitization to the organ specific uveal pigment that as a result of trauma to the uvea had been destroyed and absorbed. The pigment was assumed to induce the formation



FIG. 28. ENDOGENOUS ALLERGY.

Angioneurotic edema that could be experimentally elicited by injection of autogenous urinary proteoses.

therapeutic results with this substance. Trasoff and Meranze, Vaughan, Tuft and Brodsky and many others had no success. On the other hand Liebman and Bigland, Darby and Whitehead, Eichenlaub, Gate, Burgess and others reported some good results.

How are these widely divergent opinions to be explained? On the basis of our own investigations we venture the following conclusion: It is chiefly in cases of endogenous allergy that allergens (primary or secondary) are likely to

⁵⁹ BURGESS, N. Brit. M. J. 1: 914, 1933.

⁵⁰ Gate, J. Acta dermat. ven. col. 18: 413, 1937.

of organ-specific antibodies with consequent sensitization of the remaining uveal structures and of the opposite eye. Woods⁵²¹ supported this hypothesis by demonstrating that patients with sympathetic ophthalmia usually give positive skin reactions to uveal pigments, while control subjects give no reactions. On the basis of these studies, he employed uveal pigment as a therapeutic agent in the treatment of this disease, and reported good results.

According to Verhoeff and Lemoine,⁵²² hypersensitiveness to lens protein may be considered as the possible cause of endophthalmitis phaco-anaphylactica. After an operation on the lens of the eye, lens substance is liberated, and this material brings on a phaco-anaphylactic inflammation that prevents complete healing after the cataract extraction. Courtney⁵²³ reported that such patients gave positive skin reactions to lens protein. Burky⁵²⁴ demonstrated that rabbits that had been allergized to a lens-toxin combination developed typical endophthalmitis following injection of lens protein into the anterior chamber of the eye. This was recently confirmed by Scobee and Slaughter.⁵²⁵ Burky and Woods⁵²⁷ utilized this knowledge for prophylactic and therapeutic purposes. They found that desensitization with lens proteins in patients who gave positive reactions to lens extracts before operation, tended to ameliorate or totally inhibit such postoperative inflammations.

Furthermore, certain forms of keratitis parenchymatosa are said to be of endo-allergic origin. Both Loew and Frieberg describe such cases occurring postoperatively. These were cases of keratoplasty in which extremely severe noninfectious parenchymatous inflammation of the cornea set in ten to fourteen days after operation. It was assumed that the patient had been allergized by absorption of corneal protein released in the course of the first operation, and that the second operation (keratoplasty, iridectomy) had elicited allergic inflammation of the cornea. Loewenstein is of the opinion that interstitial keratitis appear-

ing in the course of trachomatous processes of long duration is to be attributed to absorption of corneal protein altered as a result of local nutritional disturbances.

(2) *Altered Cutaneous Protein as an Endogenous Allergen*

Not only blood serum but also tissue fluid may act as an endogenous allergen. Thus, Whitfield⁴⁹⁷ reported a case of acute vesicular



FIG. 29 ENDOGENOUS ALLERGY

Diffuse urticaria appearing ten days after severe abrasion of skin over sternum

dermatitis in which the serous discharge, trickling over normal skin areas, produced a fine vesicular eruption, while the patient's serum did not produce any reaction on his own skin. From this observation, the author concluded that a human being may become allergic to the products of his own broken-down tissues. On the basis of a number of such clinical findings, Whitfield claimed that the generalized papulovesicular eruptions sometimes seen following severe scratching and/or irritating

⁵²¹ WOODS, A. C. *Allergy and Immunity in Ophthalmology*. Baltimore: Johns Hopkins Press, 1933.

⁵²² VERHOEFF, F. H., and LEMOINE, A. N. *Am J Ophth* 5: 700, 1922.

⁵²³ COURTNEY, R. H. *Ibid* 12: 20, 1929.

⁵²⁴ SCOBEE, R. G., and SLAUGHTER, H. C. *Ibid* 27: 49, 1944.

therapy of a localized patch of chronic dermatitis are attributable to hypersensitiveness to tissue products that have become foreign to the body. The same holds good for urticaria appearing eight to ten days after an abrasion (Fig 29) or a severe vaccinal reaction (Fig 30) and for disseminated rashes that sometimes follow irritating local treatment of varicose ulcers or severe scratching of a dermatitis on the lower part of the leg (based on circulatory disturbances etc.) (Brown^{52a}). Whitfield called this phenomenon *autosensitization*.



FIG 30 ENDOGENOUS ALLERGY

Erythematous urticarial eruption occurring eight days after height of severe vaccinal reaction

Hecht Sulzberger and Weil⁵⁷ succeeded in producing organ specific sensitization to homologous skin in rabbits by daily intramuscular injections of minced rabbit skin provided increasing doses of *Staphylococcus* toxin were given simultaneously for its synergistic effect. Positive precipitin reactions were obtained. Hopkins and Burky⁵⁸ advance the hypothesis that certain dermatoses of unknown cause especially on the hands may be due to a comparable mechanism: local sensitization to epi-

dermal keratin or a product of keratin combined with *Staphylococcus* toxin liberated by organisms of low grade virulence growing in the skin. They suggest the name *keratid* for this lesion. The concept of the so called *dermatid* (pp 736-783) also postulates *autosensitization* to altered cutaneous protein.

Hampton and Cooke^{5,6} found that in the majority of cases of allergic dermatitis the patients are reactive to human dander extract—prepared from human dandruff and rendered histamine free—and that their serums contain skin sensitizing antibodies to human dander. Other allergics rarely and normal persons never react in this way. Therefore these authors are inclined to believe that there is a relation between allergic dermatitis and dander sensitivity. Whether this sensitiveness is a cause or a result of the eczematous lesions has not as yet been determined. However there is some evidence favoring the idea that these patients become secondarily sensitized to their own skin protein. It is noteworthy that there is no relationship between sensitivity to human dander and that to other animal danders.

Whether the id eruptions—such as epidermophytids, leuroids and bacterids—can properly be considered as phenomena of allergization or whether these conditions are caused by infectious or toxic agents will be discussed later in greater detail.

(3) Other Altered Organ Proteins as Endogenous Allergens

While the two preceding sections have dealt with ophthalmic and cutaneous protein respectively because there is some detailed knowledge of these mention must be made of observations concerning unrelated organs. The reason so little is known about the internal organs as sources of endogenous allergens is that the evidence can be only indirect comprising clinical findings. Thus disappearance of cutaneous or other allergic manifestations following surgical removal of a diseased organ may not be convincing proof of an endo-allergic mechanism. Furthermore methods of antibody determination are possible only in those few instances in which the endogenous allergens can be isolated. Thus Read Heilbrunn

and Liebert⁵²⁷ employed complement fixation methods to demonstrate that after insulin shock therapy in patients with schizophrenia, the brain tissue is altered, as evidenced by the presence of circulating antibodies specific for the white matter of the brain. Lewis⁵²⁸ showed that the alcoholic extract of rabbit brain, activated by a foreign protein (horse serum), is antigenic in the rabbit, this being the first

monkey or sheep brain, with egg white, horse or hog serum as "conveyors," along with *Mycobacterium tuberculosis* or *Micrococcus phlei* in aquaphor. Flocculation test revealed cross reactions between brain and testis, and to a lesser extent, between brain and kidney.

The following clinical examples strongly suggest the possibility of an endo-allergic mechanism. In a case of resistant urticaria, a

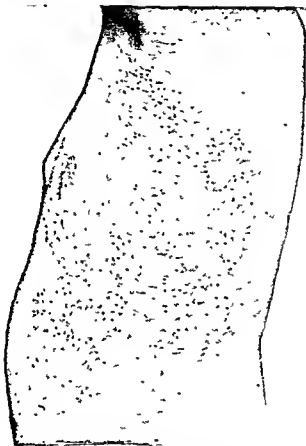


FIG 31 ENDOGENOUS ALLERGI

Generalized urticarial exanthem of three months' duration in patient of 70 years with carcinoma of rectum. After extirpation of neoplasm, rash disappeared

demonstration of isoantigenicity of a tissue lipid. The antibrain sera reacted on complement fixation with the brain (and testes) of different animal species, but not with any other organs; hence, brain lipoids are assumed to be iso-antigenic. Similar results were obtained in monkeys by Kopeloff and Kopeloff,⁵²⁹ using

hydatiform mole was ultimately discovered and its removal was promptly followed by complete cure. FIGURE 31 shows an urticarial exanthem in a patient 70 years of age with a carcinoma of the rectum. This eruption disappeared after extirpation of the neoplasm.

Barber¹⁶⁵ and von Bergmann⁴⁹³ are of the opinion that hepatic diseases particularly may lead to the production of endogenous allergens.

We realize of course that clinical results in these cases do not prove that the resorbed

⁵²⁷ READ, C. F., HEILBRUNN, G., and LIEBERT, E. J. *Nerv. & Ment. Dis.*, 90: 117, 1939

⁵²⁸ LEWIS, J. H.: *J. Immunol.* 41: 397, 1941

⁵²⁹ KOPELOFF, L. M., and KOPELOFF, N. *J. Immunol.* 48: 297, 1944

material acted as an allergen and not as a toxin. Future investigation involving skin testing with the suspected tissue protein as well as confirmation by antigen antibody reactions will be necessary before such cases can properly be classified as endogenous allergies.

e) HORMONAL ENDOGENOUS ALLERGY

Even with our present limited knowledge the endocrine hormones would seem to act as endogenous allergens quite frequently. This may occur either during functional alterations or as the result of actual pathologic changes of the endocrine glands. Inasmuch as such functional changes as menstruation and pregnancy far outnumber diseases of the endocrine system, allergic manifestations are much more often observed in association with changes of the first named type. Hence we are able to consider these in some detail while other hormonal allergies can receive only brief discussion.

(1) Female Sex Hormones as Endogenous Allergens

Allergic manifestations associated with menstruation, ovulation and pregnancy comprise such varied clinical pictures as migraine, asthma, acne and certain forms of dermatitis. The first question to be considered is of course whether or not these conditions are of auto-toxic or endo-allergic origin. This can best be answered by examining separately the conditions in menstruation and pregnancy.

Menstrual Allergy—Geber⁵²⁰ must be given credit for first demonstrating by experimental methods that there is some special substance circulating in the blood when menstrual urticaria appears. He was able to show that urticarial attacks can be provoked during the intermenstruum by intravenous injections of blood serum taken from the patient during the premenstrual flare of the skin lesions; the same serum elicited no reactions in controls. These findings were confirmed by Lichter⁵²¹ and Harrison⁵²². Geber⁵²³ contributed an even more important discovery, namely that the disturbances incident to menstruation can be cured by systematic injections of blood serum

taken during the exacerbation of the skin lesions, asthma or other symptoms.

Similar favorable therapeutic results were reported—independently in part from those of Geber—by Hopkins and Kesten⁵²⁴, Malinin⁵²⁵, Harrison⁵²² and Salen⁵²⁶. For this purpose Geber recommended intracutaneous administration of 0.2 to 0.4 cc. of serum (preserved with 0.3 per cent phenol) every other day. The injections are to be carried out according to the depot method of Lehner and Rajka¹⁸—four injections into the same skin site. Salen employed menstrual discharge collected during the first hours of menstruation before it becomes definitely sanguineous.

Zondek and Bromberg⁵²⁶ hold that the therapeutic response of cases of pruritus vulvae to administration of estrogenic hormone is plausibly explained as a hyposensitization since small quantities are effective and large doses may cause exacerbations.

The senior author³⁵⁷ reported a case of dermatitis dysmenorrhoeica that appeared three to four days before each menstrual period (Figs. 32, 33). At this time a substance was found in the patient's blood that elicited severe immediate as well as delayed reactions when injected into her skin (Fig. 34). No reactions were observed in controls. When an intervening pregnancy interrupted ovarian activity there was an almost complete remission of objective signs and subjective symptoms.

In 3 cases of dermatitis seen by the senior author in which the lesions were localized on the hands and forearms and definitely flared before each menstrual period, the skin condition readily yielded to intracutaneous injections of autogenous serum withdrawn during the height of the eruption.

The same method was employed by us in the treatment of some 40 cases of acne menstrualis. This condition is characterized by a definite flare of the lesions prior to or during the menstrual period (Figs. 35, 36). Cameron⁵²⁵ and the writers have had good therapeutic results with autogenous premenstrual serum in men-

⁵²⁰ GÉBER, J. *Dermat. Ztschr.* 32: 143, 1921. B. C. *J. Dermat. St.* 26: 1939.

⁵²¹ L. LICHTER, A. *Dermat. Wechnscr.* 9: 847, 1924.

⁵²² HARRISON, W. T. *J. A. M. A.* 100: 738, 1923.

⁵²³ GÉBER, J. *Med. K.* 31: 1203, 1913.

⁵²⁴ HOPKINS, J. G. and KESTEN, B. M. *Arch. Dermat. & Syph.* 29: 38, 1934.

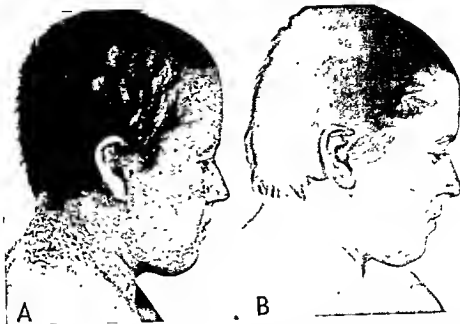
⁵²⁵ MALININ, A. J. *Dermat. Wechnscr.* 83: 1861, 1925.

⁵²⁶ ZONDEK, B. and BROMBERG, Y. M. *J. Allergy* 16: 1, 194. *J. A. M. A.* 127: 669, 1945.

⁵²⁷ LEBACH, E. *Inte. Nat. Clin.* 2: 160, 1939.

⁵²⁸ CAMERON, J. M. *Penn. J. Anal. M.* 43: 709, 1940.

strual migraine. Complete clinical relief has also been obtained by the senior author in two in degree, could be elicited by an injection of folliculin during the intermenstruum. The



ENDOGENOUS ALLERGY DERMATITIS DY-MENORRHOICA

FIG 32. Flare before and during menstrual period

FIG 33 Complete remission after temporary X-ray castration

patients with menstrual asthma and one with severe menstrual rhinopathy. The following remarkable case of premenstrual vomiting complicated by diabetes and controlled by injections of autogenous serum is worthy of mention:

A 13 year old girl with severe diabetes requiring 45 units of insulin daily, had such severe premenstrual vomiting that the usual amount of insulin caused an alarming hypoglycemic reaction. This occurred during three consecutive months. Due to the fact that menstruation was somewhat irregular, the date could not be anticipated and precautionary reduction in insulin dosage instituted. Autogenous premenstrual serum was obtained and administered in doses of 0.2 cc after the cessation of menstruation. At the next menstrual period only slight vomiting occurred and at the following one the patient was without symptoms. About eight months later premenstrual vomiting recurred, but it was not as severe, and two courses of injections were again given. During an observation period of one year since the last episode she has been free of symptoms.

Riebel⁵² observed a patient with sneezing, nasal obstruction, chills, and a temperature of 101 F. occurring one day before each menstrual period and persisting for three or four days. Exactly the same symptoms, although milder



FIG 34 ENDOGENOUS ALLERGY

Demonstration of menstrual allergen by cutaneous tests (same patient as in Fig 32). M = positive reaction to autogenous premenstrual serum. NM = negative reaction to premenstrual serum of control. N = negative reaction to autogenous intermenstrual serum. G = negative reaction to serum of gravid woman.

patient was cured by systematic treatment with this hormone.

⁵² RIEBEL, F. A.: *Ann. Int. Med.*, 9: 91, 1936.

Jahiel¹⁹⁷ suggested an interesting mechanism to account for certain menstrually determined conditions: reflux tubal menstruation was thought to provide a preparatory intraperitoneal dose of degenerating menstrual fluid while subsequent doses at the time of succeeding menses elicited asthma, rhinopathy, colic, and anaphylactic hepatic crises.

It might seem quite simple to decide the question of allergy versus toxicosis by testing

of an endogenous allergen if only the patient—and not the controls—reacted. This distinction holds in those cases in which the skin represents the shock organ as in dermatitis, dysmenorrhoea, and menstrual urticaria. However, in other forms of menstrual allergies in which the shock organ is not the skin (e.g., menstrual asthma and migraine), a negative skin test does not rule out the existence of a menstrual allergen. Although both possi-



ENDOGENOUS ALLERGY

FIG 35 Acne vulgaris with regular exacerbations two to four days before each menstrual period

FIG 36 Disappearance of acne (without local treatment) after two courses of intracutaneous injections of autogenous blood serum taken at time of exacerbation of condition

the patient intracutaneously with her own premenstrual serum or with menstrual secretion. There is definite evidence of the existence of a toxin lethal for female rats in the menstrual discharges of parous women, especially in the endometrial debris (Smith and Smith⁵¹⁰). The decisions would be in favor of the toxin theory if both the patient and the controls reacted to the intradermal injection of premenstrual blood serum when made during the intermenstruum. But the evidence would favor the assumption

ilities must be granted in principle. It is often difficult to determine in an individual case whether one is dealing with a hormonal endogenous allergy on the basis of an antigen-antibody reaction with a nonallergic hypersensitiveness (pathergy) or with a menstrual toxin. Properly performed skin tests with the steroid hormones (see below) will frequently provide convincing evidence. We are also conducting antihormone determinations in an attempt to differentiate between menstrual allergy and toxicosis.

Zondek and Bromberg⁵³⁶ have notably

⁵¹⁰ SMITH O. W. and SMITH G. V. S. *Proc. Soc. Exptl. Biol. & Med.* 55: 285, 1944.

advanced our knowledge regarding this subject, which they refer to as "endocrine allergy." They tested 165 women intracutaneously with 0.1 mg. of the following steroid hormones in 0.1 cc. of a specially prepared olive oil: crystalline estradiol, estrone, progesterone, pregnandiol, testosterone, androsterone, and desoxycorticosterone acetate. In 27 cases of known or suspected allergic disease (including asthma, rhinopathy, chronic urticaria, angioneurotic edema, certain dermatitides, migraine, psoriasis, and certain ophthalmologic conditions), in which symptoms appeared or were aggravated in relation to menstruation, 70 per cent showed positive skin reactions to one or more of the hormones. Comparable results were obtained in cases of pruritus vulvae and acne related to menstruation, of premenstrual tension, and of allergic diseases and pruritus vulvae related to the menopause. Positive reactions appeared in 3 to 5 hours, and persisted as an erythematous, slightly elevated papule at least 0.5 cm. in diameter for 24 hours or more. Many of the reactions that faded sooner could be made positive by the subcutaneous injection of 1 mg. of the test hormone 24 hours later—the "recurrent test reaction." In several cases, "retarded" reactions appeared at the site shortly before or with the appearance of menstrual bleeding, even as long as 18 days later, presumably due to an antibody against the hormonal allergen formed when the sex hormone was at its maximal level in the body. In some cases as little as 0.0001 mg. (0.1 γ) was capable of eliciting a reaction. Personal and family histories of allergy and high blood eosinophilia were frequent in those with positive cutaneous tests. Practically no reactions were obtained in normal women at any point of the menstrual cycle, in dysmenorrhea, in various allergic diseases without relationship to menstruation or menopause, in pregnancy, and in toxemia of pregnancy.

Passive transfer was successful with the serum of two cases in which it was attempted. The antibody was thermostabile, and no precipitins or complement fixation antibodies were demonstrated.

In three cases, generalized reactions consisting of vomiting, urticaria, dizziness, migraine, diarrhea, fever, metrorrhagia, and the like, were produced by the test dose which was con-

sidered too small to elicit direct hormonal or toxic effects.

Desensitization was attempted with various hormones in 44 cases, and was successful in 22, and satisfactory in 13.

The authors point out that endocrine allergy is a rare condition, and the cases were specially selected. Although the question is not settled, they do not believe that endocrine allergic disturbances are conditioned merely by an overproduction of hormones.

Phillips⁴⁴ showed that certain allergic women who suffer from premenstrual headache, tension, and associated dysfunctional ailments exhibited sharply positive reactions to intradermal testing with 0.02 cc. of a 1:5 dilution of Synapoidin (Parke, Davis). This is not an estrogen, but depends for its action on the presence of potentially functional ovarian tissue. Those women showing positive reactions were relieved of their symptoms by intracutaneous desensitization with the same preparation in doses up to 0.3 cc. of the 1:5 dilution.

In our opinion the following facts also favor the idea of an allergy: (1) Cases of menstrual urticaria, in which attacks were provoked during the intermenstruum by injection of premenstrual serum (Géber, Lichter, and Salén). (2) Dermatitis dysmenorrhoeica and menstrual urticaria in which local reactions were induced with premenstrual blood only in the patients themselves, but never in other women (Urbach). (3) Several cases of menstrual asthma where it was possible to perform passive transfer of the hypersensitiveness to menstrual secretion (Salén⁴⁵). (4) An observation that an anaphylactic shock caused by an injection of estrone (theelin), was thereafter regularly followed by a recurring syndrome of urticaria, sneezing, and asthma shortly before each menstrual period (Waldrott⁴⁶).

As regards the source of the menstrual allergen, Géber is of the opinion that it is produced by disturbances in the endocrine functions of the ovaries. Salén, on the other hand, believes that the endogenous allergens originate from the endometrium broken down during the menstrual cycle. In this connection, it might

⁴⁴ PHILLIPS, E. W. *Southwest Med J.* 27: 141, 1943.

⁴⁵ SALÉN, E. B. *Arbeten från Sabbatsbergs Sjukhus*, 1935.

⁴⁶ WALDROTT, G. L. *discussion to Cripe*⁴⁰

be pertinent to mention those rare cases of acne and dermatitis observed by the authors that manifest themselves at the time of the rupture of the graafian follicle. These patients responded readily to appropriate hormonal therapy. Here too one may consider the possibility of ovarian substances acting as endogenous allergens.

Allergy Due to Pregnancy—As early as 1908 Rosenau and Anderson⁵⁴ demonstrated that guinea pigs can be allergized to extracts of guinea pig placenta. These authors suggested the possibility of autosensitization and based an explanation of eclampsia on these experiments. More recently Yamada⁵⁵ demonstrated that guinea pigs could be specifically sensitized to the protein of eclamptic placentas by means of the serum of eclamptic patients. From these experiments he concluded that puerperal eclampsia is an allergic phenomenon caused by a specific reaction between the abnormal protein of the eclamptic placenta and maternal antibodies to this protein. See gal and Loeb⁵⁶ found that the injection of anti placenta serum into pregnant rats was followed by fetal death due to degeneration of the placenta.

During recent years attempts have been made to interpret the so called toxemias of pregnancy as allergic in nature. The fetus as well as the placenta were variously considered to act as the endogenous allergen. This theory was based in part on the fact that during pregnancy the organism—and especially the skin—shows a definite hypersensitivity to substances originating in the fetus and also to placental protein. The serum of pregnant women possesses the capacity of proteolytic action on placental protein. Further more after injection of this protein it is possible to demonstrate specific antibodies in the blood of pregnant women.

Another example of the altered reactivity of the gravid organism this time due to an endogenous hapten may be found in the following observations. Pregnant women give decidedly weaker reactions to intracutaneous injections of organ extracts than do nonpregnant women or than men. But as the exten-

sive studies of Gans⁵⁷ have shown addition of serum from pregnant women to the injected organ extract reverses the results that is the organ extract plus pregnancy serum brings on far stronger local reactions in pregnant than in nonpregnant women. It seems therefore that pregnancy serum contains a substance to which the pregnant organism is hypersensitive. This substance might be considered an endogenous hapten since pregnancy serum alone is not capable of eliciting these skin reactions. This view conforms with Jegorow's observation that only pregnant women give skin reactions to split products of placental protein obtained by a special lysate method.

Starting from the hypothesis that fetal protein may act in the maternal organism as an allergen against which antibodies are formed the senior author⁵⁷ injected fetal extract intracutaneously in a series of patients. Normal women and those in the first few months of pregnancy gave strong papuloerythematous skin reactions in twenty four hours while pregnant women in the final trimester gave negative or only very slightly positive reactions. These results can be explained only on the basis of the assumption that the gravid organism eventually acquires a specific anergy to fetal proteins. It is interesting to note how similar this mechanism is to that of the cutaneous sensitiveness of gravid women to colostrum (see above).

Mention should also be made here of the good results obtained in the dermatoses of pregnancy by means of systematic injections of the serum of normal pregnant women. The effects of this therapeutic measure may be explained by the fact that the blood in these patients contains an abnormal amount of endogenous allergens that are neutralized by the antibodies in the serum administered.

According to Finch⁵⁸ nausea and vomiting accompanying pregnancy are due to the patient's hypersensitivity to the secretion of her own corpus luteum of pregnancy. Finch holds that this hypothesis is proved by the following facts: (1) Pregnant women suffering from this syndrome give strong immediate skin reactions to 0.02 cc of progesterin. (2) Several

⁵⁴ ROSENAU, M. J. and ANDERSON, J. F. *Hyg. Lab. Bull.* 45 U. S. Pub. Health Serv. 1908.

⁵⁵ YAMADA, K. I. *Jap. J. Obst. & Gynec.* 23: 111, 1940.

⁵⁶ SEGAL, B. C. and LOEB, E. N. *Fed. Proc.* 2: 99, 101, 1943.

⁵⁷ URBACH, E. *discuss. on* Heilmann and Schiller *Klin. Wchnsch.* 6: 925, 1927.

⁵⁸ FINCH, J. W. *J. A. M. A.* 111: 1368, 1938.

of the pregnant patients who gave three or four positive reactions to progestin, intradermally administered, subsequently (as late as five weeks after the injection) reported that whenever they became severely nauseated, the site of injection flared. (3) The symptoms could be alleviated or completely controlled by injections of graduated doses of progestin. Finch's results could not be confirmed by Zondek and Bromberg.³³⁵

(2) Other Hormones as Endogenous Allergens

Numerous reports testify that individuals have been proved to be sensitive to such endocrine products as insulin, pituitrin, thyroid, pancreatin, and epinephrine. The present discussion is confined to experimentally confirmed observation of cases in which the patient is hypersensitive to the endocrine product itself, and not to the animal protein from which it is derived nor to the diluent in which it is dissolved (such as corn oil or peanut oil). Harten and Walzer³⁴³ have thoroughly reviewed this topic.

It was Tuft³⁴⁰ who first advanced unequivocal proof of specific hypersensitiveness to endocrine products. He established the existence of allergic hypersensitiveness to insulin by means of skin tests and by demonstrating the presence of specific circulating Prausnitz-Kuestner antibodies to this substance. These findings were confirmed with respect to hypersensitiveness to insulin by Sammis³⁴¹ and Lasch³⁴²; in regard to pancreatic extract by Criepe³⁴³, to epinephrine by Dumm³⁴⁴; to solution of posterior pituitary by Simon and Ryder.³⁴⁵ The demonstration by Selye and his collaborators³⁴⁶ that under certain experimental conditions overdose with desoxycorticosterone acetate elicits in rats a polyarthritis which histologically resembles that seen in acute rheumatic fever, may well be explained as an endogenous allergy to this

hormone of the adrenal cortex (Urbach³⁴⁷), although definitive proof is lacking.

It should be pointed out that endogenous allergies due to endocrine products can sometimes be manifested as a hypo- or insensitiveness. Thus, although insulin resistance is associated with a number of clinical factors and has given rise to several hypotheses as to its mechanism, Martin et al.³⁴⁸ in reviewing the literature up to 1941, call attention to the frequency with which allergy is associated with this condition. Precipitins to insulin and positive passive transfer with the serums of insulin-resistant patients have been demonstrated (Lerman,³⁴⁹ Root³⁵⁰). In explaining the mechanism of insulin resistance in infection, Root³⁵⁰ has suggested that the latter may not merely stimulate the antigenic mechanism in such a way as to produce antibodies to the specific invading organism but may stir up antibodies to insulin itself—a clear instance of parallergy. It is quite conceivable that substances in the blood that inhibit the action of insulin, the so-called "insulin antagonist," may actually be antibodies to this hormone.

In the study of autogenous organ-specific allergization, special significance must be attributed to the antihormones. This term is applied by Collip to substances that appear in the serum of animals and human beings undergoing prolonged treatment with anterior pituitary, gonadotropin, thyroxin, or other endocrine extracts. Collip and his associates hold that the antihormones are true hormones with an antagonistic effect. Thompson³⁵¹ is of the opinion that they are immune bodies of unusual type, the hormonal substances acting as antigens. These hormonal antigens are probably complex in nature, for the hormone can be separated by suitable methods from the carrier substance, which is antigenic, while the hormonal portion is not, and may therefore be considered as a haptén. Werner³⁵² found that in animals refractory states were produced to the thyrotropic principle by doses too small to

³³⁵ HARTEN, M., and WALZER, M.: *J. Allergy* 12, 72, 1940.

³³⁶ TUFT, L.: *Am. J. M. Sc.* 136: 707, 1938.

³³⁷ SAMMIS, F. E.: *J. Allergy* 6: 387, 1938.

³³⁸ LASCH, F.: *Med. Klin.* 31: 973, 1933.

³³⁹ CRIEPE, L. H.: *J. Allergy* 12: 154, 1941.

³⁴⁰ DUMM, J. F.: *Presn. med. argent.* 28: 303, 1941.

³⁴¹ SIMON, F. A., and RYDER, C. F.: *J. A. M. A.* 66: 512, 1936.

³⁴² SELYE, H., SYLVESTER, O., HALL, C. E., and LEBOND, C. P.: *J. A. M. A.* 124: 201, 1944.

³⁴³ URBACH, E.: *J. A. M. A.* 124: 731, 1944.

³⁴⁴ MARTIN, W. P., MARTIN, H. E., LYSTER, R. W., and STROUSE, S.: *J. Clin. Endocrinol.* 1: 357, 1941.

³⁴⁵ LERMAN, J.: *Am. J. M. Sc.* 207: 334, 1944.

³⁴⁶ ROOT, H. F.: in discussion of Greene, J. A., and Keoben, G. F.: *J. A. M. A.* 121: 153, 1943.

³⁴⁷ THOMPSON, K. W.: *Physiol. Rev.* 21: 583, 1941.

³⁴⁸ WERNER, S. C.: *Proc. Soc. Exper. Biol. & Med.* 34: 390, 392, 1936; *Endocrinology* 22: 291, 1938.

have any stimulating effect but large enough to act as immunizing agents. A number of other observations suggest similarities between antihormones and antibodies. Thus, Twombly⁵⁶³ pointed out that nearly all the substances producing antihormones are protein in nature, while nonproteins like estrin fail to do so in the rabbit. However it must be granted that such non protein hormones as the adreno cortical and parathyroid hormones also produce refractory states. It is possible that these act as haptens. Serum fractionation reveals that the antihormone factor is present in the globulin fraction, equally divided between the pseudoglobulin and euglobulin portions (Harrington and Rowlands⁵⁶⁴). The site of production of antihormone substances, like that of immune bodies, appears to be the reticuloendothelial system (Gordon, Kleinberg and Charipper⁵⁶⁵) and is similarly affected by "blockage" of this system by trypan blue. About 7 to 10 days is required after injection of the stimulating preparation for the formation of an antihormone in effective quantities (compare the latent period in experimental allergization). Finally, Zondek believes that the antihormones constitute immune bodies of a character hitherto unknown in serology, neither antibodies, since they fail to give rise to *in vitro* reactions, nor "hormones with reverse properties," but par taking of some of the characteristics of both. According to Joel,⁵⁶⁶ the body normally does not employ antihormones as a regulatory mechanism and they are formed only when heterogenic hormones are administered. In clinical practice, the formation of antihormones, even with long continued hormone therapy, will not lead to fastness except with anterior pituitary preparations, cortin parathyroid hormone and chorionic gonadotropic principle, such as extracts of mare urine.

These antihormones apparently explain the observed loss of responsiveness to such extracts, and are also capable of making other animals, previously untreated, refractory to these extracts. It should be pointed out that anti-

hormones, like antitoxins but unlike other antibodies, reduce the specific sensitiveness of an organism. However, the question as to whether the antihormones are immune bodies has not been settled. A full discussion will be found in the papers of Thomson, Colip and Selye⁵⁶⁷ and Thompson⁵⁶⁸. The anti gonadotropic factor has been thoroughly considered by Zondek and Sulman⁵⁶⁸.

Another important fact in connection with endogenous allergy to hormones is that antihormones such as antithyrotropic substance have been detected⁵⁶⁷ in the serum of normal untreated animals of various species, as well as of normal human beings. Furthermore, antihormones have been produced by injecting sheep pituitary extract in sheep or by implanting rat pituitary in rats. If it is possible to sensitize human beings and animals to autogenous hormones (as demonstrated by the appearance of antihormones), it would seem obvious that pathologically altered endocrine organs could all the more readily produce substances to which the organism might become hypersensitive. Thus Urbach⁵⁶⁹ has observed cases of urticaria that did not yield to therapy until a concurrent thyroid disturbance (such as toxic goiter and thyrotoxicosis provoked by iodine) was eliminated. In this connection the research of J. T. King on neurocirculatory asthenia is interesting, in that he showed the condition to be frequently characterized by great sensitiveness to injection of epinephrine. By injecting this substance, he reported, the characteristic symptoms of the disorder were reproduced. Hence "it is likely that men suffering from this condition are sensitive to their own adrenalin."

Sulzberger⁴ extends the scope of this concept when he writes

If human beings and animals can become sensitized to organ specific factors when these are administered from without cannot the organ specific factors which the organs themselves are producing within the individual also on occasion be liberated and slightly altered and thus produce autogenous organ specific sensitization? Is it not possible that these sensitivities to specific substances derived from the human pancreas the human liver etc. all within the human being may

⁵⁶³ TWOMBLY G. H. *Endocrinology* 20 311 1936

⁵⁶⁴ HARRINGTON C. R. and ROWLANDS I. W. *Biochem. J.* 31 2019 1937

⁵⁶⁵ GORDON A. S. KLEINBERG W. and CHARIPPER H. A. *Proc. Soc. Exper. Biol. & Med.* 36 484 1937

⁵⁶⁶ JOEL C. A. *Schweiz. med. Wchnschr.* 71 1011 1941

⁵⁶⁷ THOMSON D. L. COLIP J. B. and SELYE H. *J. A. M. A.* 116 132 1941

⁵⁶⁸ ZONDEK B. and SULMAN F. *The Antigonadotropic Factor* Baltimore: Williams & Wilkins 1942

give rise to organ-specific antibodies which may then be able, on occasion, to attack the specific organ substances *in vivo* and to damage the particular organ *in situ*.²

Definite confirmation of the present attempts to demonstrate the existence of hypersensitiveness to organ-specific autogenous products might yield quite unexpected results. Certain conditions suggestive of allergy (especially those presenting the clinical pictures of urticaria, angioneurotic edema, and dermatitis, and also, in certain cases, rhinopathy and migraine), but in which it has been impossible to prove an underlying allergic mechanism, may eventually be explained on this ground.

f) PHYSICAL ALLERGIES

Recent experimental and immune-biologic investigations permit the assumption that at least some of the patients with so-called physical allergies are sensitive to a modified form of their own protein. In other words, the action of physical agents (cold, heat, pressure, etc.) so alter the body's protein (generally of the skin) that it acquires antigenicity and becomes an endogenous allergen.

Karady⁵⁶⁷ reported a series of animal experiments dealing with the pathogenesis of physical allergies. The importance of these studies seems to warrant description of them. (1) Guinea pig serum was exposed to cold (-5°C) or to heat (56°C) for one and a half minutes and was then injected in a group of normal guinea pigs. Three weeks later reinjection of similarly treated serum caused anaphylactic shock, but only when the serum used had been exposed to the same physical condition. (2) Exposure of the hind legs of guinea pigs to cold (-5°C) or to heat (56°C) followed in three weeks by injection of serum previously exposed to cold or to heat, respectively, resulted in anaphylactic shock in the correspondingly treated group, but not in the cross-treated group. (3) Similar exposure of the hind limbs of the guinea pigs, followed by re-exposure to cold or heat after three weeks, also resulted in anaphylactic shock. Cross experiments were again negative.

It should be pointed out, however, that

Richardson⁵⁶⁸ was unable to confirm these results.

In this connection Burky's⁵⁶⁶ ingenious experiments are of interest. Rats can be allergized to extract of rat muscle mixed with staphylococcus toxin. These animals thereby became hypersensitive not only to rat muscle but to trauma as well, probably because of liberation in the tissue of substances identical with the rat muscle extract.

The experiments of Karady are based on the assumption that the exposure of the organism to physical forces may lead to chemical-structural changes in the protein of the plasma or cells, and that these changes may suffice to bring about denaturation of the protein of the organism, thus transforming it in effect into a protein foreign to the organism. The denatured protein so produced may act as an allergen and may thus lead to antibody formation.

This new evidence does not, of course, indicate that the same mechanism is operative in all cases belonging to the classification of physical allergy. As instanced elsewhere,⁴⁷⁰ physical hypersensitiveness may be due to pathergic response, — i.e., there is no specific antigen-antibody mechanism involved. Roth and Horton⁴⁷¹ have shown that the symptoms in such cases are probably elicited by the release of histamine from the cells, as a direct result of the trauma per se. Of course, further investigation may possibly unite both concepts on an allergic basis, if an endogenous allergen can be demonstrated in all such cases.

Aside from these animal experiments, several clinical immunologic studies seem to suggest the probability of an endogenous origin in some instances of physical allergy. Sézary, Horowitz, and Rivoire⁵⁷² reported the case of a patient who after exertion suffered from an urticarial-hemorrhagic exanthem as well as from pains in the joints. These same symptoms could be elicited experimentally by means of intravenous injections of a proteose extracted from the patient's urine. Furthermore,

⁵⁶⁶ RICHARDSON, E. H., JR. *Proc. Soc. Exper. Biol. & Med.* 45: 787, 1940.

⁵⁶⁷ KARADY, E., HERMAN, M. F., and GOTTLEB, P. M. *Arch. Dermat. & Syph.* 43: 360, 1941.

⁵⁶⁸ ROTH, G. M., and HORTON, B. T. *J. A. M. A.* 110: 686, 1936.

⁵⁷² SÉZARY, A., HOROWITZ, A., and RIVOIRE. *Bull. et mém. Soc. méd. d'hop. de Paris* 47: 760, 1931.

several authors reported that they were able to perform passive transfer of hypersensitiveness to physical agents such as cold and heat (Harris Lewis and Vaughan Lehner and Rajka Liebner Prieto and others). The reason why so few successful passive transfers have been described is undoubtedly the fact that it is very difficult to isolate the endogenous allergen involved. However this problem can perhaps be solved as Melzer and Wlassics⁵⁷³ have shown by using the tissue antibodies contained in blister fluid (Urbach Koenigstein method). If the usual procedure fails we recommend the so called reverse technic in which the endogenous allergen is first produced locally by exposing an area of skin in a normal subject to cold heat or pressure. Then the *tissue antibodies* contained in the fluid from a blister raised by a cantharides plaster on the skin of the patient allergic to the specific physical agent are injected. A positive reaction is manifested by a large wheal.

The effect of exposure to cold in the production of autohemagglutination has already been mentioned. Benians⁵⁷⁴ speaks of cold antibodies since injection of his patients' serum caused arterial spasm in rabbits with lysis of erythrocytes and rapid death. Dameshek⁵⁰⁹ warns against chilling of patients with virus pneumonia and other conditions in which a cold agglutinin is found. Aside from hemolytic anemia and icterus autohemagglutination may be responsible for gangrene of the extremities (Stats and Bullowa⁵⁷⁵) acrocyanosis (Helwig and Freis⁵⁷⁶) Raynaud's syndrome and a shock like state (Benians⁵⁷⁴).

3 HETERO ENDOGENOUS ALLERGENS

This group comprises as previously mentioned the allergens that arise within the body but are not derived from the body's own substances. The chief representatives of this category are infectious and parasitic agents.

a) INFECTIOUS ALLERGY

One of the earliest known facts in relation to allergy was that such organisms as bacteria

viruses and fungi are able to allergize their host—that is to induce the formation of specific antibodies. The extent to which the disease symptoms in infectious and parasitic allergies are based on this mechanism is still unsettled. The decision is especially difficult because the infectious antigens have the capacity of multiplying and also because they are often primary cytotoxic agents. In dealing with these antigens therefore one encounters situations far more complex and far more obscure than those obtaining in allergic conditions due to primarily harmless proteins that are incapable of multiplying.

Furthermore it is conceivable that the infectious agents do not themselves act as antigens and that the latter consist rather of intermediary products resulting from the action of the bacteria on body protein.

Infectious agents can become antigenic in three ways

(1) They can enter into the organism from without multiply there induce antibody formation and thus elicit allergic reactions. This is the case in all acute infectious diseases.

It was von Pirquet⁵ who first called attention to the fact that many of the clinical findings in acute infectious diseases correspond with the symptoms seen in serum sickness and experimental anaphylaxis. He referred to such clinical observations as the incubation period of some eight to ten days followed by an exanthem the regularity of the course and the recurrence of the manifestations in stages. According to von Pirquet the incubation period is not the time during which the agents multiply but rather the time necessary for the formation of antibodies to the bacterial protein. But even in diseases with a short term of incubation the possibility of allergy cannot be ruled out on this basis alone. It must be borne in mind that a rapid course may be run especially by diseases due to ubiquitous agents in these cases allergization may have taken place previously.

(2) Infectious agents may not begin to have an allergizing influence until they have existed within the organism for some time. This is generally the case in chronic infectious diseases (such as tuberculosis and syphilis) as well as in focal infections.

Allergic phenomena in chronic infectious

* MELZER M and WLASSICS T Arch f Dermat u Syph 1 6 157 1937

* BENIANS T H C J Lab & Clin Med 29 1001 1944

* STATS D and BULLOWA J G M A Ch Int Med 72 429 1943

* HELWIG F C and FREIS E D J A M A 123 626 1943

diseases are well known. Thus, the phases of immunity, alternating with evident signs of disease, are definite indications of an altered reactivity. This has been appreciated for a long time in relation to the skin manifestations of tuberculosis or tertiary syphilis, with their characteristic peripheral extension and central healing. The tuberculoid structure is the histologic expression of a bacterial-allergic origin.

Focal infections play an especially important rôle in bacterial allergization. Extensive clinical experience has convincingly shown that these foci are capable of primarily causing and/or maintaining a state of hypersensitivity. This is the underlying mechanism in many cases of chronic asthma ("intrinsic asthma" of Rackemann) and in some cases of chronic urticaria and chronic dermatitis, as well as in certain rheumatoid diseases and arthritides.

Dr. H. P. Steiger described to the senior author a case illustrative of such a mechanism, who had a rather severe angioneurotic edema eight days after the onset of infectious mononucleosis. For many months thereafter, he suffered from repeated attacks of pharyngitis, each time accompanied by urticaria. Hypo-sensitization with autogenous streptococcal vaccine was carried out and resulted in complete cure of the urticaria, despite occasional recurrences of pharyngitis.

(3) Infectious agents can bring on allergic phenomena by means of endogenous reinfection. When bacteria, fungi, and viruses reach allergized skin from remote sites, by way of the blood, disease phenomena follow that are known as "id" eruptions, these include the tuberculids, trichophytids, syphilids, and leu-rids. This explanation is substantiated by the finding of living organisms in the blood and tissues, provided examination is made at the proper time, i.e., shortly before the generalized eruption appears. It may be re-emphasized that a highly sensitized tissue is a prerequisite, as proved by the strong skin reactions to such substances as tuberculin and trichophytin.

Furthermore, Whitfield¹⁹⁷ and Barber²⁷⁷ called attention to disseminated allergic cutaneous eruptions in association with impetiginous streptococcal infection of the skin or subcutaneous tissue, and proposed the term

"streptococcids." Similar clinical pictures are occasionally observed in patients with boils, carbuncles, or abscesses. Here the evidence points strongly to a similar allergic mecha-



FIG 37 ENDOGENOUS ALLERGY

Disseminated vesicular dermatitis (left thigh, leg, and forearm) occurring about ten days after onset of impetigo in region of knee, and probably due to resorption of altered cutaneous protein. Healed without treatment in few days.

nism, with the staphylococcus as the bacterial antigen causing the generalized eruption (Fig. 37).

b) PARASITIC ALLERGY

It is a well-established fact that parasites such as echinococci, tapeworms, roundworms, and trichinae are able to allergize their host (Casoni, Botteri, W. Jadassohn, Fuellenborn, Morenas, Rackemann and Stevens, and others).

¹⁹⁷ BARBER, H. W.: *Lancet* 2, 363, 1929.

However, which of the symptoms in naturally occurring infestations may be regarded as allergic? Some of the pathologic manifestations can be attributed to the purely physical and nonallergic effect of the parasites (as a cyst of the echinococcus in the lung or a cysticercus in the brain). Other clinical manifestations are certainly due to primarily toxic substances produced by some parasites.

On the other hand, the endogenous allergic mechanism may be operative in those cases of asthma, rhinopathy, conjunctivitis, intestinal

colic, pruritus, urticaria and angioneurotic edema in which the patients are infested. The allergic origin is dramatically demonstrated when, for example, a typical anaphylactic shock (with or without asthma) follows the rupture of an echinococcal cyst in the course of an operation. Other clinical examples will be found in chapter XIX.

To what extent allergy is responsible for the marked eosinophilia accompanying many infestations is still unknown.

CHAPTER X

ANTIBODIES

A. NATURE OF ANTIBODIES

ANTIBODIES* may be defined as specifically reacting substances produced by the body in response to the parenteral or enteral introduction of an antigen. Paul Ehrlich's original idea was that each antibody reaction was due to an independent antibody. He spoke, therefore, of agglutinins, precipitins, lysins, opsonins, antitoxins, anti-enzymes, reagins, and bactericidal and virucidal antibodies. Zinsser,⁵⁵ Gay,¹¹ Dean, and other authorities, on the other hand, champion the "unitarian" theory with reference to the identity of antibodies. They maintain that a common antibody is at the base of the various antibody functions, and that it is the character, localization, and other environmental conditions of the antigen that determine whether the antibody is to function in a neutralizing, precipitating, complement-fixing, or other capacity. In other words: when in a given case the antigen is a toxin, it is neutralized by the antibody; when the antigen is a colloidal particle, it is precipitated; when it is a bacterium, it is agglutinated; and so forth. This is well illustrated by the experiments of Alperstem,⁵⁷³ who showed that bacteria can be agglutinated by the serum of pollen-sensitive patients, provided the bacteria are first coated by pollen antigen. Even the theory that the skin-sensitizing antibodies are quite different from precipitins was disproved by Cohen and Weller.⁵⁷⁴ Likewise, Landsteiner and Chase⁴⁷² noted that when cutaneous sensitivity was induced in guinea pigs by means of intradermal injections of simple chemical compounds, circulating antibodies could be demonstrated by the Schultz-Dale technic; they held that the two specific sensitization effects could not be without a fundamental relationship. Moreover, Putter as well as Haurowitz⁴⁵² hold that, from the technical viewpoint, it is altogether misleading to speak of precipitins, agglutinins,

tropins, etc., since these terms are in fact no more than indications of the methods by which the same antibody may be demonstrated.

The present authors also adhere to the unitarian school of thought. It must be pointed out, however, that—at least with regard to the skin reaction—the *antitoxins are in a separate and distinct category* from the other antibodies. Antitoxins are, of course, specific antistances produced within the body in response to toxins. The presence of antitoxins is manifested not in a positive cutaneous antigen-antibody reaction, but in the failure of any local inflammation to appear, as evidence of a neutralization of the specific toxin (Examples of the toxin-antitoxin reactions are the Schick diphtheria skin test and the Dick scarlet fever skin test). This is to be explained by the fact that while the bacterial toxins are primarily toxic for the skin and other tissues, neutralization is effected by union with the antitoxin, so that no cellulotoxic effect ensues.

The significance of antibodies in anaphylaxis and human hypersensitiveness, particularly pollinosis, has recently been reviewed by Samms.¹¹⁵

The chemistry of antibodies is briefly discussed on page 109. It need only be repeated here that antibodies consist of modified serum globulins. Pauling and Campbell⁴⁷⁹ were able to produce antibody *in vitro* by denaturing and renaturing normal serum globulin in the presence of various antigens. Significantly, the antiserum for pneumococcus polysaccharide type III so created not only precipitated the specific antigen, but also agglutinated type III pneumococci. The nature of the alteration in the globulin by which it is converted into antibody has been the subject of considerable investigation. Ehrlich's specific receptor hypothesis or "side chain" theory is of only historic import and has been abandoned. Numerous attempts to demonstrate antigenic, chemical, and physical differences between immune and non-immune globulin have been uniformly unsuccessful. While no definitive answer is possible in the present state of

* Synonyms: reagins, anaphylactins, sensitizins.

⁵⁷³ ALPERSTEM, B. B. - *Ann. Allergy* 3: 119, 1945.

⁵⁷⁴ COHEN, M. B., and WELLER, R. P. - *J. Allergy* 12: 242, 1941.

knowledge it would appear that the antibodies are newly formed chemical complexes synthesized as a result of the action of normal intracellular enzymes differing from globulin in the spatial arrangement of its constituent amino acids. It is assumed that the templating action of the absorbed antigen is responsible for the specific modification of the globulin during intracellular synthesis. The persistence of the antibody matrix may explain why the reinjection of one antigen may cause the reappearance of antibodies to the same as well as to other antigens (the anamnestic reaction) and also the acquisition of acquired resistance without the presence of large amounts of circulating antibody (Cannon⁵⁸⁹)—thus possibly accounting for some of the phenomena of 'heteroallergy'. Burnet⁵⁹⁰ however disagrees with the templating hypothesis maintaining that simultaneously with the destruction of the antigenic particle such modification in structure and activity of the intracellular proteinases takes place as to provide a pattern and a scaffold on which the new protein is constructed. Sevag⁵⁹¹ advances still another hypothesis attributing enzymatic action to the antigen which in its action converts the globulin into antibody globulin just as the action of an enzyme on a substrate forms reaction products. According to this view for which Sevag adduces considerable evidence the neutralization of an antigen by its antibody is comparable to the specific inhibition of an enzyme by the reaction products.

In any case the importance of the protein reserves and of adequate dietary protein in the formation of antibodies has been experimentally demonstrated (Cannon⁵⁸⁸). This is of great clinical importance in relationship to resistance to various infections (Madden and Whipple⁵⁹², Cannon et al.⁵⁸⁴, Cannon⁵⁸⁵) and accords with the observed increase in susceptibility to infectious diseases resulting from an

adequate diets in certain populations in both World Wars.

Today two types of antibodies are arbitrarily recognized: the humoral and the fixed. The former circulate freely in the blood; the latter are cellular or sessile. However it is widely believed that all antibodies arise primarily from the cells (histogenic formation), a portion then finding their way into the blood stream. It is generally accepted that only a reaction between antigens and fixed antibodies produces a cellulotoxic effect while a reaction with the humoral antibodies is not accompanied by a tissue response. This conclusion is based on the results of experiments that show (1) that the tissues react anaphylactically even when the blood plasma has been freed from antibodies and (2) that bloodless isolated organs of allergized animals react to the addition of the antigen (Schultz Dale experiment). It is not as yet conclusively known which organs and which types of cells take part in the creation of antibodies. The older concept attributed antibody formation to the reticulo endothelial system. However evidence has arisen recently indicating that the site of antibody formation may be the lymph node with the lymphocyte playing an essential part (Ehrlich and Harris⁵⁹³).

The reticulo endothelial system appears to be operative in both of the major anti allergic methods: (1) in hyposensitization stimulation of the system gives rise to increased production of antibodies and release of these into the blood; (2) in deallergization the blockade of the system causes an inhibition of antibody production (for further details see p. 201).

Aside from the capillary endothelium of the blood vessels the reticulohistiocytes of the skin may be of special importance in the formation of antibodies. This view is supported by the fact that it is possible to transfer a hypersensitivity passively by means of the contents of skin blisters. With regard to increased antibody production following stimulation of the reticulo endothelial system there are several reports on histologic investigations (Monacelli⁵⁹⁴, Urbach and Wiedmann⁵⁹⁵) that lead to

⁵⁸⁹ CANNON P. R. *J. Lab. & Clin. Med.* 28: 177, 1942.

⁵⁹⁰ BURNET F. F. *The Production of Antibodies*. Melbourne: Macmillan, 1941.

⁵⁹¹ CANNON P. R. *J. Immunol.* 44: 107, 1942.

⁵⁹² MADDEN S. C. and WHIPPLE G. H. *Physiol. Rev.* 20: 194, 1940.

⁵⁹³ CANNON P. R., WISSLER R. W., WOODEN DGE R. L. and BENNETT E. P. *Ann. Surg.* 120: 14, 1944.

⁵⁹⁴ CANNON P. R. *J. A. M. A.* 128: 360, 1945.

⁵⁹⁵ EHRLICH W. E. and HARRIS T. N. *J. Exper. Med.* 76: 33, 1942.

⁵⁹⁶ MONACELLI M. *Giorn. ital. dermat. e sif.* 71: 126, 1930.

⁵⁹⁷ URBACH E. and WIEDMANN A. *Med. Klin.* 29: 742, 1933.

the conclusion that irradiation causes an increase in the histiocytes of the skin. The first definite proof that increased antibody production follows reticulo-endothelial stimulation were the animal experiments of Urbach and Nékám, Jr.⁵⁴⁹ These authors subjected allergized guinea pigs to unfiltered soft roentgen rays, exposing either the entire skin or the spleen alone; subsequent administration of an ordinarily lethal shock dose was tolerated by these animals without symptoms. Similarly, Alföldy⁵⁵⁰ showed that irradiation of the spleen brings on an increase in the reticulo-endothelial function, manifested by an enhanced tuberculin reaction, as well as by the presence in the blood of procutines, substances that enhance the tuberculin reaction. These experiments—together with the aforementioned histologic findings—permit us to entertain the opinion that stimulation of the reticulo-endothelial system by roentgen rays produces a change in the allergic state, resulting in enhanced resistance, owing to the release of increased numbers of cellular antibodies into the blood.

Inhibition of antibody production by means of blockade of the reticulo-endothelial system was suggested by the experiments in which such blocking with dyes, India ink, etc., prevented anaphylactic shock in allergized animals (Jaffe, Lewinson, and Hughes, Moldovan and Zolog, Gay and Clarke). Klinge employed this method of blockade to combat local protein hypersensitiveness, such as the Arthus phenomenon, and H. Meyer prevented passive anaphylaxis by applying the blockade method prior to allergization. Urbach and Nékám, Jr.⁵⁴⁹ showed that inhibition of antibody production in highly desensitized animals resulted in a return to a considerably higher state of sensitivity. These authors found that when animals received trypan blue (the dye serving to block the reticulo-endothelial system) simultaneously with the desensitizing injections, the protective effect of the latter was partially cancelled. These animals now presented shock symptoms after a threefold lethal dose, whereas a sevenfold lethal dose had been required before the addition of the trypan

blue to the injection. The explanation appears to be that the blockade of the antibody-producing apparatus decreases the number of antibodies reaching the blood and available for neutralizing the antigens.

Mention should also be made here of the interesting experiments performed by Sabin⁵⁶³ with the so-called marked antigen, such as alum-precipitated dye protein. The appearance of antibodies in the serum corresponds with the time when the dye protein is no longer visible within the cells. Sabin deduces, therefore, that the cells of the reticulo-endothelial system normally produce globulin, and that antibody globulin represents a synthesis of a new kind of protein under the influence of antigen.

On the other hand, Bunting⁵⁶⁴ has long maintained that antibodies are formed by the lymphocyte. This is supported by a number of observations. Kass⁵⁶⁵ showed that human lymphocytes contain gamma globulin, and Dougherty, Chase, and White⁵⁶⁶ that agglutinins and hemolysins in mice occur in high titer in the lymphocytes. However, it was Ehrich and Harris⁵⁶⁷ supported by Rich⁵⁶⁸ who found that antibody production was accompanied by lymphoid hyperplasia, and that the antibody content was greater in efferent than in afferent lymph when the antigen is injected locally. The regional lymph node shows a sharp increase in size and is not only high in antibody titer, but is stimulated to an increased production of lymphocytes which themselves contain antibody in a much higher concentration than the surrounding lymph (Harris and Ehrich⁵⁶⁹). Ehrich and Harris⁵⁶⁶ grant the phagocytic and digestive function of the micro- and macrophages of the reticulo-endothelial system, but state that it is essential only in the preliminary break-down of formed antigens, the products of this digestion then reaching the antibody-forming cells elsewhere. On this basis they explain the observations concerning reticulo-

⁵⁴⁹ URBACH, E., and NÉKÁM, L., JR. *Klin. Wochenschr.* 25: 1069, 1936.

⁵⁵⁰ ALFÖLDY, J. *Science* 101: 317, 1945.

⁵⁶³ DOUGHERTY, T. F., CHASE, J. H., and WHITE, A. *Proc. Soc. Exper. Biol. & Med.* 57: 295, 1945.

⁵⁶⁴ RICH, A. R. *ibid.* 32: 1395, 1925.

⁵⁶⁵ HARRIS, T. N., and EHRLICH, W. E. *J. Bact.* 49: 291, 1945.

⁵⁶⁶ EHRLICH, W. E., and HARRIS, T. N. *Science* 101: 25, 1945.

⁵⁴⁹ URBACH, E., and NÉKÁM, L., JR. *Klin. Wochenschr.* 25: 1069, 1936.

⁵⁵⁰ ALFÖLDY, J., BERNÁTH, Z. VON, and ENGELMAYER, E. VON: *Ztschr. f. Tuberk.* 55: 40, 1936.

endothelial "blockade" and dye-protein considered above. These investigators hold that lymphocytes are the major (or perhaps the only) local cells responsible for antibody synthesis. Ehrlich's studies are of more than academic interest since they open a new vista in attacking allergic diseases by possibly increasing the antibodies by stimulating lymphocytic activity.

Recent investigations have led to the highly important conclusion that the antibodies appearing as a result of parenteral therapy are unlike those that appear as the result of a specific hypersensitiveness per se. Cooke et al.^{597-599, 197} present evidence tending to show that the serum of every treated hay fever patient contains two distinct antibodies, whereas only one such antibody is demonstrable in the serum obtained before therapy. The latter antibody is thermolabile and skin sensitizing, and remains locally in an injected site for weeks, it fails, however, to transfer the hypersensitiveness and cannot pass through the placenta. The other antibody (produced both in allergic and—as shown by Loveless⁵⁹⁹—in nonsensitive persons by the parenteral administration of ragweed extract) is thermostable, incapable of sensitizing normal skin, but antigen binding, and disappears in less than twenty-four hours from an inoculated cutaneous site, it shows good transfer properties and can be placentally transmitted. By these means it is possible to differentiate between the natural skin sensitizing and the artificially produced blocking antibody. Frank and Gelfand⁶⁰⁰ failed to find this antibody in other immune sera but only in those of ragweed treated patients. A precipitation method for its detection was described by Hampton and his collaborators⁶⁰¹ and should simplify future investigations along these lines. Sulzberger⁶ objected to the terms "blocking" or "inhibiting" as vague and preferred to call them neutralizing antibodies that is, antibodies capable of neutralizing the specific antigen *in vivo* but not of sensitizing

the skin. Loveless thinks that the term neutralizing is not much better and suggests calling them thermostable antibodies because in this way they can be distinguished from the thermolabile ones. Harley⁶⁰² confirmed the existence of the inhibitory or blocking antibody of Cooke. He demonstrated that the blocking takes place between the antibody and the allergen and not between the antibody and the skin cells. The presence of thermostable neutralizing (immune) antibodies in the sera of both a treated and an untreated dog with spontaneously occurring hay fever was demonstrated by Wittich.^{75a}

Loveless⁶⁰³ believes that within the limitations of the method and individual differences in sensitivity to the allergen and susceptibility to the H substance the titer of the thermostable antibody in hay fever is a measure of clinical response to therapy. While Scully and Rackemann⁶⁰⁴ and Gelfand and Frank⁶⁰⁵ confirmed the existence of the thermostable blocking antibody they could find no correlation between the amount of it produced as a result of treatment and the clinical relief of symptoms. On this basis they concluded that the therapeutic effects of pollen hyposensitization are not due to the production of blocking antibodies. Cooke⁶⁰⁶ is in substantial agreement, although believing that the blocking antibody may not be devoid of all effect. He suggests that its presence for certain fractions of allergens, especially the protease or second fraction of ragweed pollen, may permit larger dosage without the danger of constitutional reaction.

Langner and Kern⁶⁰⁷ described a new form of treatment on the basis of Cooke's discovery. They employed serum from hay fever patients who had been treated successfully by the usual method. The serum was concentrated by the lyophile process encouraging results in other hay fever patients are reported. However, up to the present this method has not achieved wide spread clinical acceptance.

Loveless⁶⁰⁸ showed that after therapy has

⁵⁹⁷ COOKE R A, BARNARD J H, HENALD S and STULL A J. *Exper Med* 62 733 1935

⁵⁹⁸ COOKE R A, LOVELESS M H and STULL A. *ibid* 66 689 1937

⁵⁹⁹ LOVELESS M H. *J Immunol* 28 15 1940

⁶⁰⁰ FRANK D E and GELFAND H H. *J Allergy* 14 273 1943

⁶⁰¹ HAMPTON S, JOHNSON M C, ALEXANDER H L and WILSON K S. *ibid* 14 227 1943

⁶⁰² HARLEY D. *J Path & Bact* 44 589 1937

⁶⁰³ LOVELESS M H. *J Allergy* 15 311 1944

⁶⁰⁴ SCULLY M A and RACKEMANN F M. *ibid* 12 549 1941

⁶⁰⁵ GELFAND H H and FRANK D E. *ibid* 15 337 1944

⁶⁰⁶ COOKE R A. *ibid* 15 212 1944

⁶⁰⁷ LANGNER F H and KERN R A. *ibid* 10 1 1938

⁶⁰⁸ LOVELESS M H. *South Afr J* 33 869 1940

been discontinued, the inhibiting antibody rapidly disappears from the serum, and the tolerance of the tissue to the antigen is lost. According to Sherman and Stull,³⁹⁵ however, years of treatment will bring about a qualitative change in the character of the antibody: the capacity to transfer sensitiveness is decreased, while the ability to neutralize the antigen is increased.

The "inhibins" of Cooke might very well be identical with the "dereagins" of Lehner and Rafka.¹⁷⁷ This term was employed by the two Hungarian investigators to designate certain inhibitory substances in the blood of allergic individuals: these substances have the capacity to diminish and sometimes even to inhibit specific skin reactions. A pertinent example was contributed by Hilber.⁴⁰⁹ When skin sites of tuberculin-sensitive children were passively sensitized with the serum of an egg-sensitive eczematous patient, the tuberculin reaction was completely or partially inhibited in a large percentage. This effect could be "exhausted" by previous injection of egg white antigen, in which case the tuberculin reaction was not affected.

Aside from the specific antibodies—i.e., those produced in response to specific antigens—there are also heterophile or Forssman antibodies. These may be defined as antibodies that react with antigens apparently unrelated to those originally responsible for the production of the antibodies. As is well known, Forssman⁴³⁰ found that when emulsions of the organs of certain animals (particularly the guinea pig and horse) are injected in animals of another group (especially the rabbit), there are produced not only specific antibodies to the injected antigen, but also agglutinins and hemolysins for sheep erythrocytes. It has been shown furthermore that there are varieties of heterophile antibodies other than the Forssman type. For example, injection in animals of certain bacteria and plant protein may stimulate the production of heterophile antibodies (Davidsohn and Walker⁴¹⁰; Rockwell and van Kirk⁴¹¹). The consensus in the literature seems to be that a titer of 1:16 is

the limit for normal persons. Heterophile antibodies in larger amounts are seen in infectious mononucleosis and in serum sickness.

The present state of our knowledge does not permit us to hazard an opinion as to the true significance of the heterogenic antibodies in allergic manifestations. It is interesting to note, however, that Hedin was able to prove that there was no increase in the number of these antibodies in dermatitis, and only a slight increase of them in urticaria.

In addition to the heterophile antibodies, Landsteiner and van der Scheer³⁷ pointed out that one antigenic grouping can call forth the formation of diverse antibodies. Furthermore, it has been demonstrated that intensive and/or very frequent contact with an antigen can bring about at first only partial and subsequently a total loss of specificity of the antibodies (Meissner). Thus, for example, when a rabbit receives large doses of sheep protein over a long period of time, the animal will be found to have antibodies not only to sheep serum, but also to human, horse, and swine serum. Cooke and Sherman,⁴¹² working with human serums that in passive transfer tests reacted to a number of antigens, found that an antigen often effected neutralization of biologically unrelated antigens. Hooker and Boyd⁴¹³ offered additional proof that the antibodies to a single "pure" antigen develop a broadened reactivity as time goes on. Three possible explanations are offered by these authors.⁴¹³

(1) The antibody initially formed is directed toward a dominant-determinant group of the antigen, and, progressively, additional antibodies are formed for separate minor determinants. (2) The later antibodies differ from the earlier by the presence on their molecules of additional discrete reactive groups that may differ qualitatively, the latter antibodies thus being more multivalent. (3) The third possibility is substantially an extension of the explanation offered by Landsteiner, that is, "the antibodies vary to some extent around a main pattern."

Hooker and Boyd advance experimental evidence favoring the last explanations. These facts explain—in part at least—the phenomena of metallergy and nonallergic pathergy.

⁴⁰⁹ Hilber, H. *Zschr. f. Kinderh.* 60, 522, 1939.

⁴¹⁰ Davidsohn, I., and Walker, P. H. *Am. J. Clin. Path.* 5: 455, 1935.

⁴¹¹ Rockwell, G. E., and Kirk, H. C. *Van. J. Infect. Dis.* 59, 171, 1936.

⁴¹² Cooke, R. A., and Sherman, W. B. *J. Bact.* 39, 62, 1940.

⁴¹³ Hooker, S. B., and Boyd, W. C. *Proc. Soc. Exper. Biol. & Med.* 47, 157, 1941.

Tuft and his collaborators⁶⁴ have used the method of lyophilization for preserving antibodies for two or three years without demonstrable loss of potency. This technic should prove to be of great value in storing different types of serums for use whenever required. It would thus seem possible to obtain blood from patients showing sensitivity to some unusual type of allergen and to preserve and store the serum against the time when it might be needed for experimental or therapeutic purposes. Another advantage of this process is that serums—especially those with low antibody content—can be concentrated.

B. DETERMINATION OF ANTIBODIES BY LABORATORY METHODS

1. PRECIPITATION

The earliest means of demonstrating circulating (humoral) antibodies was the method of precipitation. It was thought for a long time that the presence of precipitins was a sign of rather severe allergization. However it was later shown that specific precipitins can be found in the blood not only of marantic children but also of healthy children and even of adults following the ingestion of proteins (Tunck, Moro and Gyorgy, Strobl and Wasitzky). Hence this finding by no means indicates the presence of pathologic sensitization; it may be merely the expression of a physiologic defense reaction. On the other hand it is well known that anaphylactic responses quite often occur without demonstrable precipitins in the circulation. The reason for these discrepancies are not yet known. New and improved methods such as that of Cannon and Marshall⁶⁵ may in the near future shed light on this problem. Their technic is sharply specific and delicate enough to demonstrate the presence of precipitins in animal serums that are so weak that no visible precipitate occurs when specific antigens are added. Employing this method these authors demonstrated specific precipitins in serums from patients hypersensitive to egg protein, tuberculin and crystalline insulin. A quantitative method of determining precipitins was con-

tributed by Johnson and his collaborators.⁶¹⁶ Lowell⁷ showed that the colloidal particle technic is the most sensitive test for determining antibody.

2. COMPLEMENT FIXATION

Whether allergic antibodies can be demonstrated by means of complement fixation is a question not entirely settled. Gyorgy, Moro and Witebsky⁶¹⁸ claim to have demonstrated the presence of complement fixing antibodies to egg white in the majority of serums of eczematous children showing strong cutaneous reactions to egg white and giving positive Prausnitz-Kuestner reactions. This was possible however only in certain concentrations (called the *Rechtszone*) when high dilutions of egg white (1:30,000 to 1:1,000,000) were employed. On the other hand infants allergized intracutaneously to egg white exhibited complement deviation only when concentrated egg white was employed. It appears likely therefore that there are two different kinds of complement deviating and complement fixing antibodies: (1) those characteristic of naturally acquired hypersensitiveness and (2) those seen in cases of artificially induced allergization. Bosch, Gyorgy and Witebsky found that in cases in which the *Rechtszone* was duly established it was almost invariably possible to achieve positive Prausnitz-Kuestner reactions but never in artificially allergized children.

These findings have been confirmed by Wöringer as well as by Mueller and Brandt. The latter explain the inefficacy of concentrated egg white solutions as antigens by reason of the presence of a protective substance serving to inhibit reactions; the influence of this substance becomes negligible when high dilutions are employed.

Jaffé⁶⁸ was able to demonstrate the presence of complement fixing antibodies in cases of hypersensitiveness to fish, yeast and lentils. He employed serum and autohemolysins as well as autocomplement instead of strongly active hemolytic systems; this technic is

⁶⁴ TUFT, L., WENGER, L. J. and FRANKEL, J. J. *J. Allergy* 19: 27, 1938.

⁶⁵ CANNON, P. R. and MARSH, E. C. E. *J. Immunity* 38: 365, 1940.

⁶¹⁶ JOHNSON, M. C., ALEXANDER, H. L., ROBINSON, R. and ALEXANDER, J. H. *J. Allergy* 15: 83, 1944.

⁷ LOWELL, F. C. *J. Immunity* 4: 177, 1943.

⁶¹⁸ GYORGY, P., MORO, E. and WITEBSKY, E. *Klin. Wochenschr.* 9: 10, 1939.

⁶⁸ JAFFÉ, K. *Klin. Wochenschr.* 10: 304, 1931.

analogous with Hecht's modification of the Wassermann reaction. Whenever the complement-fixing reaction was positive, the skin tests were also positive and successful Prausnitz-Kuestner transfers were invariably obtained. Similarly Bostrom and Hellerstrom demonstrated complement fixation in a case of neurodermatitis due to hypersensitiveness to fish.

On the other hand, it has only very rarely been possible to show complement fixation in cases of hypersensitiveness to drugs (Szodoray and Gyorgy). This is probably due to the fact that it is not the drug itself but intermediary or conjugation products that act as the antigen. Since it is impossible to isolate the latter by existing methods, a true complement-fixation test cannot be performed.

One of us has undertaken a considerable number of complement-fixing experiments, these were successful in cases of hypersensitiveness to egg, milk, and pollen, but always failed in cases of drug allergy. In any event, this promising method warrants further intensive study for the development of improvements on the technic now employed. The significance of this method seems to lie in the promise that it would enable us to forego experiments on animals and human beings in many instances, and would permit us to perform large series of tests with relatively small amounts of blood serum.

3. PASSIVE TRANSFER TO ANIMALS

The classic method of passive transfer consists of injecting animals, intravenously or intraperitoneally, with the serum of hypersensitive individuals, followed twenty-four hours later by the intravenous or intraperitoneal administration of the allergen. But it is only in exceptional instances that this method succeeds (Bruck, Klausner, Kyrle, Flandin, and Tzanck). On the other hand, Lang and Dér¹⁵⁵ claim that the reverse passive transfer method gives better results. In this procedure, rabbits are first injected intracutaneously with the antigen (e.g., 0.01 Gm of quinine bisulfate); then, six hours later, 5 cc. of serum from the hypersensitive patient is administered to the animal intraperitoneally, a positive result will be typical anaphylactic shock. By this means, Lang and Dér were

able to transfer hypersensitiveness to quinine, iodine, and iodoform, and Lehner and Rajka¹⁷⁷ that to mustard oil. A similar mechanism is no doubt the basis of the Opie¹⁷⁹ experiment: specific skin reactions are evoked in nonsensitized rabbits by first injecting the antigen and then the immune serum.

While the Prausnitz-Kuestner technic of passive transfer has consistently shown itself to be of no avail in lower animals, it is successful when monkeys are used as the recipients (Caulfeild¹⁸² and Straus¹⁸¹). In this manner it was possible to transfer hypersensitiveness to pollen, horse serum, cottonseed, peanuts, and flounder from a human being to a monkey.

C DETERMINATION OF ANTIBODIES BY CLINICAL METHODS

In addition to the above methods, antibodies can be demonstrated by the passive transfer of hypersensitiveness to human beings, this can be achieved by general sensitization with antibody-containing blood, or by local sensitization with antibody-containing serum, tissue fluids, or cells.

It is necessary to distinguish between humoral and cellular transfer of hypersensitiveness. In the former type whole blood or blood serum is used, the transfer being mediated by circulating antibodies present in the blood at the time it is withdrawn. The prototype of this procedure is the Prausnitz-Kuestner method. In the second type, utilizing blister fluid, exudates, or epidermis, the transfer is accomplished by cellular antibodies. The majority of the successful transfers of this nature were achieved with the Urbach-Koenigstein method. It will be seen, as discussed further below, that these methods are biologically different. The great importance of the cellular transfer methods is demonstrated by the fact that epidermal hypersensitiveness as seen in allergic contact dermatitis can be transferred only by the blister method taking the form of a delayed reaction, and never with blood serum as an immediate reaction.

I HUMORAL PASSIVE TRANSFER

a) PASSIVE TRANSFER BY MEANS OF BLOOD TRANSFUSIONS

General allergization as a result of transfusions of large quantities of blood from aller-

¹⁷⁹Opie, E. L. *J. Immunol.* 9: 227, 1924

gic to normal human beings has been reported only in exceptional instances (Frugoni with blood taken from an asthma patient hyper sensitive to rabbit hair Ramirez with blood from an asthmatic patient hypersensitive to horse and a few others) Clinical examples of generalized passive sensitization by intravenous injections of human serum will be found on page 354

Loveless⁶²¹ showed that blood donors sensitive to ragweed pollen transferred their hypersensitivity to recipients previously not allergic to pollen The recipient's skin was the first tissue to manifest acquired hypersensitivity and the last to relinquish it

(b) PASSIVE TRANSFER BY MEANS OF BLOOD SERUM

(1) Prausnitz Kuestner Technique

Since the introduction of the ingenious idea (Prausnitz and Kuestner⁶²² De Besche) of using the skin for local allergization by means of blood serum from a hypersensitive patient it has been possible to achieve passive transfer rather constantly The specific nature of the Prausnitz Kuestner antibodies has been confirmed by Coca and his collaborators They neutralized the skin sensitizing capacity of the antibodies by adding the specific allergen to the antibody containing serum *in vitro* Further

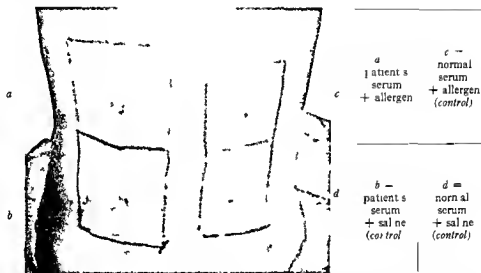


FIG 38 PRAUSNITZ KUESTNER REACTION PASSIVE TRANSFER OF HYPERSENSITIVENESS WITH BLOOD SERUM

The first planned transfusion experiments upon man were carried out by Garver.⁶ Each of 3 recipients was transfused with 500 cc of blood obtained from donors whose multiple sensitivities were demonstrated by the presence of positive cutaneous reactions and of humoral antibodies Cutaneous reactivity to such antigens as spinach dust horse dander timothy and ragweed pollen was detected in the recipients as early as fourteen hours after transfusion reached its maximum by the fourth or fifth day and largely disappeared by the fourteenth day

more desensitization of the skin sites of the Prausnitz Kuestner injections is accomplished by injecting the homologous allergen

TECHNIC The Prausnitz Kuestner test is carried out by injecting 0.1 cc of the allergic blood serum intracutaneously into the skin of the back of a normal individual and 24 hours later injecting 0.02 cc of the allergen into the same skin site (a) However it should be stated most emphatically that the reaction may not be interpreted as positive merely because a wheal surrounded by a reddened area appears after thirty minutes It is essential that all three of the following controls be negative A skin site (b) prepared by injecting 0.1 cc of allergic serum should not react to subsequent

⁶²¹ LOVELESS M H. *ibid* 41: 15-19, 1
⁶²² GARVER W P. *J Allergy* 11: 3, 1939

⁶²³ PRAUSNITZ C and KUESTNER H. *Zentralblatt Bakteriol. Orig.*
 86: pt 1, 160, 1921

injection of physiologic salt solution. Another skin site (c), prepared with 0.1 cc. of normal serum, should not react to injection of the allergen. A third site (d), prepared with 0.1 cc. of normal serum, should not react to injection of physiologic salt solution (see Fig. 38 and Table 16). Experience has shown that a nonspecific positive reaction may sometimes be elicited not only by the allergen but even by the physiologic salt solution. If these control tests were conscientiously performed, many seemingly positive Prausnitz-Kuestner transfers would prove to be nonspecific. It is also important that the recipient chosen for the test have neither a personal nor a family history of allergic disease. Hence, a relative of the patient may not be used. Arbesman and Eagle⁶² presented a thorough description of the variables involved in passive transfer experiments.

In addition to the above-mentioned controls a "syringe control" has been suggested by Simon⁶³ to eliminate the possibility of previous protein contamination of the syringe. The sterile syringes are partially filled with extracting fluid, and the plunger twisted and pushed in and out several times so as to insure intimate contact of the fluid with the inner surface of the

according to present opinion is the most definite evidence of an antigen-antibody reaction. The wheal generally appears about one hour after the injection of the antigen. Gyorgy, Moro, and Witebsky⁶¹ recommended that metameric and symmetric skin sites be used.

Distant reactions can also be elicited by oral, nasal, rectal, and other routes of administration. Of these, the oral route introduced by Freeman,⁶²⁷ then developed and popularized by M. Walzer,¹³¹ is now being widely employed. The technic is as follows: A normal recipient is given an injection of 0.1 cc. of allergic serum into the skin of the back. Twenty-four hours later the antigen is administered by mouth (Walzer), by way of the nose (Cohen et al., Sulzberger and Vaughan), or by rectum (Smyth and Stallings). A positive reaction usually appears within one hour. It must be noted, however, that this method is by no means always successful.

It is noteworthy how minute a quantity of antigen will suffice to evoke a Prausnitz-

TABLE 16—*Prausnitz-Kuestner Reaction. Passive Transfer of Hypersensitivity with Blood Serum*

Site	Injection	
	First	After 24 Hours
a	0.1 cc. of serum of allergic patient	0.1 cc. of allergen
b	0.1 cc. of serum of allergic patient	saline solution
c	0.1 cc. of serum of normal subject	0.1 cc. of allergen
d	0.1 cc. of serum of normal subject	saline solution

syringe. Only if this fluid produces equal and negative reactions in sensitized and non-sensitized skin sites is each syringe considered acceptable for use in the experiment, and then only for the particular serum tested.

Swinney⁶⁴ described a micro Seitz filter useful for the filtration of small amounts of solutions. In doing passive transfers, the serum may be drawn directly into a small hypodermic syringe and forced through the filter directly into the skin with an intradermal needle. Thus, filtration and sensitization of the sites are performed at one step, saving time and avoiding contamination.

In order to avoid a nonspecific local irritation from the injection of the antigen, the "distant reaction" may be employed (W. Jadassohn, Gay and Chant, Biberstein, Urbach, and others). This technic consists in injecting the antigen at some distance from the allergized skin site. Thus, when the result is positive, only the area prepared with the allergic serum will respond with a wheal and erythema. A response elicited in this manner is to be regarded as a focal reaction, which

Kuestner reaction. Thus, Bosch and his collaborators⁶⁵ succeeded with a 1:10,000,000,000 dilution of egg albumin. As little as 0.1 cc. of egg white by mouth sometimes suffices to evoke a distant reaction, 0.05 cc. by rectum. Even the rubbing of a piece of silk on a passive transfer site prepared with the serum of the patient allergic to silk can produce a large wheal with considerable erythema (Taub⁶⁶).

There should be an interval of some twenty-four to forty-eight hours between the injections of serum and of antigen, although this interval can be lengthened or shortened. Thus, the reaction can be elicited even when the antigen is administered within as brief a time as forty-five minutes, or after as long an interval as four to six weeks. It is even

⁶² ARBESMAN, C. E., and EAGLE, H. *J. Allergy* 10: 521, 1939.

⁶³ SIMON, F. A. *Ann. Allergy* 2: 15, 1944.

⁶⁴ SWINNEY, B. *J. Lab. & Clin. Med.* 23: 1008, 1933.

⁶²⁷ FREEMAN, J. *Proc. Roy. Soc. Med. (Laryng. Sect.)* 18: 29, 1925.

⁶²⁸ TAUB, S. J. *J. Allergy* 1: 539, 1930.

possible to inject the antibodies and the antigens simultaneously, but the results are then difficult to evaluate accurately, since the injection of the antibody containing serum may bring about a nonspecific immediate reaction that invites erroneous interpretation.

The Prausnitz Kuestner reaction almost invariably manifests itself as an immediate reaction—i.e., the local wheal formation takes place within one and a half hours. Occasionally one does observe a delayed response (appearing after five to six hours) and, rarely, a late reaction (eighteen to twenty-four hours).

The Prausnitz Kuestner reaction is not by any means positive in every case of hypersensitivity. Failure may be attributed in part to the individual reaction capacity of the recipient, it is necessary, therefore, to perform the transfer test in at least three control persons. Another common reason for a negative result is that there were insufficient free antibodies in the blood at the time of its withdrawal, this point is confirmed by the constant observation that passive transfer is always negative following a severe allergic attack. According to Lehner and Rajka, the most favorable period for taking the blood is from twenty to thirty minutes after a relatively weak exposure to the specific allergen, provided that the allergizing agent is known. The purpose of this procedure is to increase the circulating antibodies. Bizzozero and Ferrari reported that when they followed the procedure suggested by Lehner and Rajka they succeeded in passively transferring hypersensitivity to iodoforn.

The success or failure of passive transfer does not depend upon the clinical severity of a given case (as, for example, on the extent of an allergic exanthem), but primarily and essentially upon the quantity of antibodies available in the blood at the time of the test. Under certain conditions—apparently when a food or a drug is not a primary but a secondary allergen (see p. 115)—passive transfer can be achieved only by means of the reversed technique: first the antigen is administered, and several hours later the antibody containing serum is injected intracutaneously. Thus, Kenedy⁴⁸⁷ was able to transfer hypersensitivity to phenolphthalein in this manner: a normal recipient was given the drug twice daily by mouth, and four hours after the last

dose he received intracutaneous injections of allergic and normal serum. Twenty-four hours later a late reaction appeared only in the skin site of the injection of allergic serum; another control subject, not having received phenolphthalein, gave no reaction after the injection of allergic serum. A Walzer⁴⁸⁹ succeeded in transferring hypersensitivity to peanuts in the same way: a normal recipient ate about 15 to 30 Gm of peanuts half an hour later, 0.01 cc of allergic serum was injected intracutaneously, whereupon a local reaction appeared. This method corresponds to the reverse passive transfer in animals as performed by Lang and Der (p. 116). A comparison of the sensitivity of the reversed reaction with that of the classic passive transfer reaction (Prausnitz Kuestner) revealed that the reversed reaction is still strongly positive at levels of antigen and antibody concentration at which the passive transfer reaction begins to fail (Wright and Hopkins⁴⁹⁰).

Autopassive transfer is the designation given by Cowie⁴⁹¹ to the following method. When the skin of an allergic individual fails to react to the intradermal injection of the allergens to which he is clinically sensitive, passive transfer of the patient's own blood into his own skin will cause the skin to react to the allergen. Although Marton⁴⁹² was unable to confirm these findings, Mason and Swineford⁴⁹³ established this phenomenon as an unequivocal fact, but referred to it as (reversed) passive local autosensitization. Allergic patients were given one or more intracutaneous injections of autogenous serum. The subcutaneous injection of antigen at a remote site a few minutes to 24 hours later elicited whealing, itching reactions at the prepared skin sites, appearing 1½ to 5 hours after the injection and persisting from 1 to 24 hours. Only 4 of 15 patients reacted, and not at all skin sites. In three instances, desensitization was noted as manifested by negative reactions to pollen injections that produced wheals on untreated

⁴⁸⁹ WALZER A. Arch. Dermat. & Syph. 38: 1 1938.

⁴⁹⁰ WRIGHT G. P. and HOPKINS S. J. J. Path. & Bact. 53: 243 1941.

⁴⁹¹ COWIE D. M. Ann. Int. Med. 11: 949 1937.

⁴⁹² MARTON S. J. Allergy 11: 266 1940.

⁴⁹³ MASON J. R. and SWINEFORD R. O. Jr. Southern M. J. 36: 324, 1943.

parts of the body. Swineford and Mason⁶¹ also reported another type of "desensitization of passively autosenitized sites." A hay fever patient who had received five injections of a dilute ragweed extract every third day was injected, one hour after the last dose, with 0.1 cc. of his own serum. Large urticarial wheals appeared at the site of these injections. Another ragweed injection six days later was followed by generalized urticaria except in those sites that had reacted one week before. In 5 other patients this reaction could not be elicited. Unfortunately, Mason and Swineford call this phenomenon autosenstization. This term should be used only for sensitization to autogenous allergens. As pointed out by Epstein,⁶² the original term autopassive transfer is more descriptive and will avoid unnecessary confusion with true autosenstization, which was considered in the preceding chapter.

It must be mentioned in conclusion that the test subject is not entirely unscathed by the passive transfer procedure. The senior author has seen cases in which localized and even quite extensive dermatitides occurred from eight to ten days after a positive Prausnitz-Kuestner reaction—conditions surely attributable to allergization by the administered antigens. It is obvious what the consequences might be in the case, for example, of a person who had been allergized to neoarsphenamine or to bismuth and who subsequently contracted syphilis. As Sulzberger discovered, this danger of sensitization to arsenicals can be obviated by injecting the antigen intravenously in the test subject immediately after the positive skin reaction. The senior author also observed that recipients are especially susceptible to allergization when they happen to be suffering from a bacterial infection (e.g., staphylo- or streptodermas) at the time of the passive transfer.

(2) Dilution Test

Once the presence of skin-sensitizing antibodies has been determined by passive transfer (Prausnitz-Kuestner test), it is at times desired to gain some quantitative estimate of their titer. This is useful, for example, in

following the antibody content of the serum during specific hyposensitization therapy. The dilution test is a quantitative modification of the passive transfer technic, employing serial dilutions of the antibody-containing serum and a fixed amount of antigen, and allowing them to react in the recipient's skin. The patient's serum must be withdrawn under sterile conditions, without addition of a preservative, and should prove negative on serologic testing for syphilis.

TECHNIC The exact dilution of the serum and the dose of antigen to be employed depend on the anticipated antibody titer of the serum and the nature of the antigen. In cases with low antibody titer, the serum is diluted with physiologic saline solution in ratios of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, while in cases with high antibody titer the dilutions may begin with 1:100 etc. An amount of 0.1 cc. of each dilution is injected intracutaneously in nonallergic recipients. Twenty-four or forty-eight hours later, 0.1 cc. or less of an appropriate dilution of the antigen extract (one capable of eliciting a positive passive transfer reaction) is injected intracutaneously into each of the prepared skin sites. Positive reactions resemble those of the passive transfer test. The end point is taken to be the greatest dilution of serum (e.g., 1:32) producing a positive reaction.

(3) Neutralization Tests

The neutralization tests constitute another means of titrating the amount of skin-sensitizing antibodies, and depend upon the reactions obtained when skin sites in normal recipients are prepared with mixtures of antibody-containing serum plus the allergen in various proportions, and then tested with the allergen. The smallest amount of allergen that inhibits the activity of the skin-sensitizing antibodies in the mixture provides a measure of the antibody concentration. Two types of methods must be distinguished: (1) those that neutralize the antibody, and (2) those that neutralize the antigen. In the former method, the antigen and the serum of the allergic patient are mixed *in vitro*. The consequence is that the antibodies are neutralized, so that the serum loses its capacity to transfer the hypersensitivity. Therefore this substance, when injected into a normal control subject, is incapable of eliciting the Prausnitz-Kuestner reaction.

TECHNIC Varying dilutions of a carefully standardized antigen extract are prepared, and the same quan-

⁶¹ SWINEFORD, O. J., and MASON, W. R., Jr. *J. Immunol.* 41: 293, 1941.

⁶² EPSTEIN, S. *Ann. Allergy* 2: 247, 1944.

tity (e.g. 0.2 cc.) of each is added to a measured volume (e.g. 0.8 cc.) of the allergic serum in sterile vials. The protein nitrogen content of each mixture is readily calculable. The skin sites of a nonallergic recipient are prepared by injecting 0.1 cc. of each mixture intracutaneously. This may give rise to immediate reactions which should be disregarded. Twenty-four or forty-eight hours later the antigen injection is given intracutaneously in the skin sites. It is apparent that only those sites will react that receive in the mixture a proportion of antigen insufficient to neutralize completely the skin sensitizing antibodies contained in the serum. The end point therefore is taken to be the last positive reaction since at this point there is com

2 CELLULAR PASSIVE TRANSFER

a) PASSIVE TRANSFER TO HUMAN BEINGS BY MEANS OF BLISTER FLUID (URBACH KOENIGSTEIN TECHNIC)

The frequent failure of the passive transfer methods that depend upon the humoral antibodies in the blood is not surprising to those who subscribe to the concept that all antibodies are of cellular origin. It seems logical therefore to assume that especially in localized

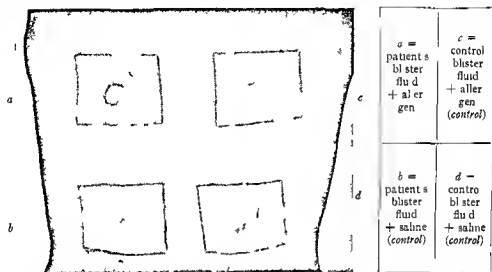


FIG. 39 URBACH KOENIGSTEIN REACTION. PASSIVE TRANSFER OF HYPERSENSITIVENESS WITH BLISTER FLUID

plete neutralization of the antibody with minimal excess of antigen. Thus the antibody content of the serum is measured in terms of the amount of antigen required to neutralize it and the results can be expressed in protein units (e.g. 150 protein units required to neutralize 0.8 cc. of serum). No attempt should be paid to the size of the reactions since this depends largely on the characteristics of the recipient's skin.

In the second method of neutralization the mixture of antigen and its specific antiserum *in vitro* serves to inhibit or at least to weaken the antigenic action *in vivo*. In other words the antigen is then no longer free to elicit a cutaneous reaction in a specifically hypersensitive individual. It must be noted however that the so-called neutralization phenomenon can occur only when great care has been taken not to have an excess of antigen.

hypersensitivities such as the allergic dermatoses antibodies must be more abundant in the tissues and must thus be more readily and definitely demonstrable there than in the blood. At Koenigstein's suggestion the senior author²³ in 1924 developed the blister method in which the cellular antibodies contained in spontaneous or artificially produced bullae are employed.

TECHNIC. An amount of 0.05 cc. of blister fluid is injected intracutaneously in a normal subject who has been tested and shown not to be hypersensitive to the given allergen. When blisters are already present and of sufficient size as occasionally seen in prurigo turpentine and other dermatides their contents are aspirated by sterile technique. When there is no spontaneous blister a local allergic reaction is evoked by means of percutaneous or intracutaneous administration of the antigen in order locally to enhance the cellu

lar antibodies. A cantharides plaster is then applied to the site to raise a blister.

After the local irritation produced by the blister content has subsided (twenty four to forty eight hours) the antigen is injected intracutaneously in the same site of the recipient. A positive result is indicated by the appearance, after eighteen to twenty four hours, of an elevated reddish-brown papule that persists for about twenty four hours and then gradually disappears (so-called delayed reaction, Fig. 39). No reaction occurs at the control sites.

The necessary injections consist of blister fluid from the allergic patient and from a normal subject (raised by application of cantharides) for the preparation of

the skin sites, and of the allergen as well as of normal saline. From this it will be seen that each test requires three controls (see Table 17).

In cases of epidermal allergization, as in allergic dermatitis, it is advisable to apply the allergen percutaneously with the technic used in patch testing. A positive result is manifested by an eczematous reaction on the area covered by the patch (Fig. 40). It is also possible to attempt a distant reaction by administering the antigen by mouth or rectum (see p. 147).

When blister contents are inactivated for a half hour at a temperature of 56 C., the reaction is weaker, heating the material at a temperature of 64 C. renders the test negative.

TABLE 17—Urbach-Koenigstein Reaction. Passive Transfer of Hypersensitiveness with Blister Fluid

Site	Injection	
	First	After 24 Hours
a	0.1 cc. of blister fluid of allergic patient	0.1 cc. of allergen
b	0.1 cc. of blister fluid of allergic patient	saline solution
c	0.1 cc. of control blister fluid	0.1 cc. of allergen
d	0.1 cc. of control blister fluid	saline solution

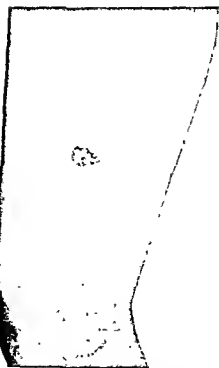


FIG. 40. PASSIVE TRANSFER OF PRIMROSE HYPERSENSITIVENESS BY URBACH-KOENIGSTEIN METHOD

Triangular shape of dermalitic reaction corresponds to area contacted by triangular portion of primrose leaf

It has often been said that the Urbach-Koenigstein reaction is a modification of the Prausnitz-Kuestner method. However, there are the following fundamental differences. The Prausnitz-Kuestner method evokes an immediate reaction of urticarial nature and of relatively short duration (wheal reaction), while the Urbach-Koenigstein method evokes a delayed reaction of inflammatory and papular nature, of rather long duration (tuberculin type reaction). Moreover, it is only with the blister fluid method that the passive transfer of allergic dermatitides in the form of eczematous contact-type reactions is possible (Fig. 41). The passive transfer of experimentally induced epidermal hypersensitivity to the simple chemical dinitrochlorobenzene has also been achieved by this method (Fig. 42). We^{63a} believe, therefore, that with the blister fluid method the presence of cellular antibodies is proved, while with the Prausnitz-Kuestner method only circulating antibodies are demonstrated.

Recently, McGuire and Shaffer^{63a} reported

^{63a} URBACH, E. Arch. f. Dermat. u. Syph. 154, 590, 1928

^{63b} MCGUIRE, J. A., and SHAFFER, B. Arch. Dermat. & Syph. in press, 1935

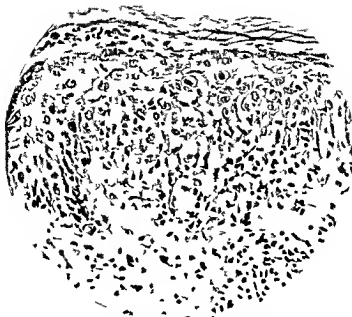


FIG 41 HISTOLOGY OF POSITIVE REACTION (ECZEMATOID TYPE) TO PASSIVE TRANSFER BY URBACH KOENIGSTEIN METHOD OF PRIMROSE HYPERSENSITIVENESS OF SKIN

Truly eczematous nature of reaction proved by *alte alto ca stare* (type of epithelial cell degeneration characteristic of acute dermatitis). Biopsy taken from reaction shown in FIG 40

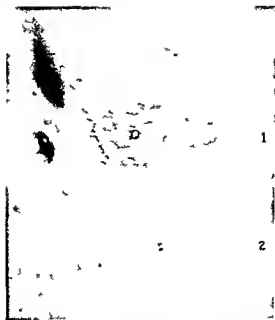


FIG 42 PASSIVE TRANSFER OF EXPERIMENTALLY INDUCED EPIDERMAL HYPERSENSITIVENESS TO DINITROCHLOR BENZENE BY MEANS OF BLISTER FLUID (URBACH KOENIGSTEIN METHOD)

Sensitizing injection at site 1 of 0.05 cc of centrifuged blister exudate from an experimentally sensitized donor. Forty eight hours later application at sites 1 and 2 of 0.03 cc of a 1:1000 solution of dinitrochlorbenzene. After twenty four hours a well marked vesicular dermatitis at transfer area (1) but only a very slight erythema at control site (2)

(Courtesy Ballestro and Moniz¹⁹⁵⁷)

successful passive transfer of sensitivity to sulfathiazole with this technic. In a case of fixed bullous eruption due to this drug cantharides blisters were raised on normal skin and also on the sites of previously healed lesions. The transfer was positive only with fluid from the blisters on sites where the dermatosis had been present and not from those on the unaffected skin. Passive transfer tests using blood serum were negative. We have stressed for some years that in cutaneous drug allergy and particularly in fixed drug eruptions, it is imperative to induce the blisters for the purpose of this test on previously involved skin areas.

It has been possible by means of the blister fluid method to achieve the passive transfer of hypersensitiveness in many cases in which the Prausnitz-Kuestner method has failed. Because the objection has been repeatedly voiced that only very few controlled cases are on record, we should like to list 42 cases reported by twenty-four workers:

- Arsenic dermatitis (Urbach⁶²)
- Neosphenamine dermatitis (Fuhs and Riehl, Jr.⁶¹ Mueger,⁶³ Riehl, Jr.,⁶¹ Schreiner⁶⁴)
- Sulfathiazole (McGuire and Shaffer⁶⁵)
- Primrose dermatitis (Perutz and Rosner⁶⁴ Urbach and Sidaravičius⁶²)
- Turpentine dermatitis (Perutz⁶² Šterbakov⁶⁴ Ensbrenner,⁶⁴ Urbach and Sidaravičius⁶²)
- Arnica dermatitis (Urbach,⁶⁶ 2 cases)
- Ammonium persulfate (van Dishoeck and Roux⁶¹)
- Atropine dermatitis (Biberstein⁶⁴)
- Orthoform dermatitis (Konrad⁶⁴)
- Nickel dermatitis (Urbach,⁶⁶ 2 cases)
- Iodoform dermatitis (Perutz⁶⁴)

- Novocain dermatitis (Santalov,⁶² Šterbakov⁶⁴)
- Flour dermatitis (Zitzke,⁶¹ Urbach)
- Asparagus dermatitis (Hajós and Mohrmann⁶⁶)
- Herring roe (Houda⁶⁶)
- Ratanhia dermatitis (Mueger⁶⁷)
- Barley dust dermatitis (Urbach and Steiner⁶⁵)
- 2,4-dinitrochlorbenzene dermatitis, experimentally induced (Ballastero and Mom,⁶⁹ 267, 269 8 cases)
- Guinea pig hypersensitiveness (Brandt and Konrad⁶⁹)
- Light hypersensitiveness (Flarer⁶⁹)
- Heat hypersensitiveness (Melczar and Wlassics,⁶⁹ 2 cases)
- Tuberculin hypersensitiveness, by means of the fluid from a papule of a Pirquet reaction (Fellner⁶⁹)
- Hypersensitiveness to typhoid bacilli (Engel and Vighiam⁶⁹)

Biberstein⁶⁴ raised the question as to whether a positive result by means of cantharides plaster may be unequivocally interpreted as a specific reaction, or whether it might be attributable to traces of the cantharides. This objection appears to have been answered by the findings of Konrad,⁶⁴ Fuhs and Riehl,⁶⁷ and Riehl,⁶⁹ for these authors inadvertently produced a specific allergization to orthoform and neosalvarsan as manifested by a generalized dermatitis in control subjects receiving injections of blister serum and antigen.

By means of passive transfer, Spain and Newell⁶⁹ confirmed the fact that specific skin-sensitizing antibodies are regularly present in blister fluid. According to Parlato,⁶⁸ the antibodies in burn blisters manifest the phenomenon of exhaustibility of reaction in passively sensitized sites.

⁶¹ FUCHS, H., and RIEHL, G., Jr. Arch f Dermat u Syph 154: 87, 1927

⁶² MUEGER, A. Zentralbl f Haut u Geschlechtskr 45: 303, 1933

⁶³ RIEHL, G., Jr. Arch f Dermat u Syph 151: 57, 1929

⁶⁴ SCHREINER, K. in Berger, W., and Hansen, K. ed.: Allergie Leipzig, Thieme, 1940

⁶⁵ PERUTZ, A., and ROSNER, R. Arch f Dermat u Syph 156: 509, 1928

⁶⁶ URBACH, E., and SIDARAVIČIUS, B. Klin Wchnschr 9: 205, 1932

⁶⁷ PERUTZ, A. Arch f Dermat u Syph 152, 615, 1926

⁶⁸ ŠTERBAKOV, I. Zentralbl f Haut u Geschlechtskr (abst.) 44: 329, 1933

⁶⁹ ENSBRENNER, G. Arch f Dermat u Syph 168: 364, 1933

⁷⁰ URBACH, E. Ztschr f Immunitätsforsch u exper Therap 55: 471, 1928

⁷¹ DISHOECK, H. A. E. VAN, and ROTX, D. J. Arch f Dermat u Syph 181: 34, 1910

⁷² BIBERSTEIN, H.: ibid 154, 555, 1924

⁷³ KONRAD, J.: ibid 165: 726, 1932

⁷⁴ URBACH, E. Zentralbl f Haut u Geschlechtskr 37: 799, 1931

⁷⁵ PERUTZ, A. Arch f Dermat u Syph 154: 206, 1927

⁶¹ SANTALOV, N. Zentralbl f Haut u Geschlechtskr 39: 413, 1932

⁶² ŠTERBAKOV, I. ibid 39: 78, 1934

⁶³ ZITZKE, E. Dermat Wchnschr 93: 1009, 1932

⁶⁴ HAJÓS, B., and MOHRMANN, B. H. U. Klin Wchnschr 8: 1074, 1929

⁶⁵ HOUDA, T. Jap J Dermat 41: 80, 1937

⁶⁶ BRANDT, R. Wien klin Wchnschr 46, 973, 1933

⁶⁷ URBACH, F. and STEINER, M. Arch f Dermat u Syph 153: 772, 1927

⁶⁸ BALLASTERO, L. H., and MOM, A. M. Rev Soc Argent de Biol 19: 10, 1913

⁶⁹ BRANDT, R., and KONRAD, J. Arch f Dermat u Syph 161: 445, 1930

⁷⁰ FLARER, F. Zentralbl f Haut u Geschlechtskr 36: 192, 1931

⁷¹ MELCZER, M., and WLASSICS, T. Arch f Dermat u Syph 176: 157, 1931

⁷² FELLNER, B. Wien klin Wchnschr 32: 936, 1919

⁷³ ENGEL, C., and VIGHIAM, M. R. Klin Wchnschr 15: 1471, 1936

⁷⁴ SPAIN, W. C., NEWELL, J. M., and MEERER, M. G. J Allergy 5: 571, 1934

⁷⁵ PARLATO, S. J. ibid 7: 571, 1936

The concept of the cellular transfer of acquired hypersensitiveness received strong support from Landsteiner's and Chase's animal experiments which also served to underline the fundamental biologic differences between this approach and passive transfer by means of blood serum. Landsteiner⁶⁶⁷ found that exudates from the peritoneal cavities of guinea pigs previously sensitized to a number of simple chemical substances would cause homologous specific skin sensitivity if injected intravenously, intraperitoneally or intracutaneously into normal guinea pigs. The nature of the antibody present in these peritoneal cells is still undetermined. Chase⁶⁶⁸ was able by a similar technic to transfer passively tuberculin hypersensitiveness after the animals had been sensitized by subcutaneous injections of killed tubercle bacilli. The peritoneal exudates were induced by intraperitoneal injections of liquid petrolatum and were found to consist mainly of large mononuclear cells. The recipients were shown to be tuberculin hypersensitive after a latent period of from two to three days following intraperitoneal injection and in about half that time after intravenous injection. Similar transfer could not be effected with the donor's serum.

b) PASSIVE TRANSFER BY MEANS OF AUTOTRANSPLANTATION (NÆGELI TECHNIC)

By means of autotransplantation Nægeli et al.⁶⁶⁹ were able to demonstrate the presence of cellular antibodies in the skin in fixed drug eruptions. For reasons not yet known it is impossible—either in human beings or in animals—to perform a successful heterotransplantation of the skin unless (in animals) the reticulo endothelial system has first been blocked by dyes or other substances. Autotransplantation on the other hand is readily accomplished.

TECHNIC. An area of fixed drug eruption that has consistently reacted with inflammation to peroral administration of a given drug (e.g. phenolphthalein) and a normal skin site are selected. Portions of each area are mutually transplanted by the Thiersch method. When healing is complete the patient is given the drug (e.g. phenolphthalein) by mouth. The reaction is

called positive when the transplanted allergic epidermis shows a flare while the transplanted nonallergic epidermis does not react.

The following successful transfers of hypersensitiveness by this method have been reported to antipyrine by Nægeli⁶⁶⁹ to phenolphthalein by Urbach and Sidaravicius⁶⁷⁰ and to potassium iodide by Fellner and Vasconcellos⁶⁷¹. A few other investigators however have failed to obtain positive reactions with the autotransplantation method. Knowles⁶⁷⁰ and our own experiments led to the conclusion that the varying results may be explained by the different intervals allowed to elapse between the transplantation and the administration of the test drug when it is given early (eight to twenty days after transplantation) the skin transplants react as they did in their original sites but when the drug is given at a later date (e.g. after two months) the transplanted skin loses its antibodies.

3. CLINICAL VALUE OF PASSIVE TRANSFER METHODS

The passive transfer tests are employed clinically for a wide variety of indications (see p. 171). The results of passive transfers must however be most carefully interpreted since patients may respond with such reactions to a great number of substances to which they have no clinical hypersensitiveness whatever (Harkavy). It must be most emphatically stressed therefore that the demonstration of specific antibodies is by no means conclusive evidence of the allergic nature of a given case. Thus as Chobot and Hurwitz⁶⁷² have shown antibodies can frequently be demonstrated in the serums of children for instance those with infantile dermatitis without any clinical manifestations of allergy following the ingestion of the respective foodstuffs. Furthermore a number of individuals show specific antibodies to foreign serum without having serum sickness. Patients with intestinal parasites usually show a very high antibody titer without manifesting any allergic phenomena. Persons with hay fever may have circulating

⁶⁶⁷ LANDSTEINER K. and CHASE M. W. *Proc. Soc. Exper. Biol. & Med.* 49: 688, 1942.

⁶⁶⁸ CHASE M. W. *ibid.* 59: 134, 1944.

⁶⁶⁹ NÆGELI O., QUERVAIN E. DE and STALDER W. *Klin. Wchnsch.* 9: 924, 1930.

⁶⁷⁰ KNOWLES F. C., DECKER H. B. and KANDLER R. P. *Arch. Dermat. & Syph.* 33: 227, 1936.

⁶⁷¹ FELLNER M. and VASCONCELLOS C. *ited by Nægeli O.* *Klin. Wchnsch.* 11: 853, 1932.

⁶⁷² CHOBOT R. and HURWITZ G. *J. Allergy* 8: 427, 1937.

antibodies not only to the pollen that causes the hay fever, but also to other pollens that elicit no clinical manifestations of disease, and even to pollens with which the patient could never have come into contact for geographic reasons. Whether the presence of such antibodies is due to the fact that one antigenic grouping can call forth the formation of diverse antibodies (Landsteiner and van der Scheer¹²⁷), or to the fact that the action of heterogenic antigens induces the production of heterophile antibodies, has not as yet been sufficiently investigated.

Furthermore, it must always be borne in mind that passive transfer—like a skin test—does not in any way indicate the degree of clinical sensitivity (Withers, Peshkin, Ratner). Nor does the absence of antibodies (negative result of the Prausnitz-Kuestner experiment) necessarily mean that a given dermatosis,

rhinopathy, or asthma is not of allergic causation. The impossibility of transferring the hypersensitiveness passively with blood serum antibodies in a given case indicates nothing more than failure to demonstrate the presence of antibodies in the circulating blood. In such instances, the presence of cellular antibodies may be established by means of the Urbach-Koenigstein blister fluid method. This is particularly the case in allergic contact dermatitis. In other types of cases, the antibody cannot be demonstrated for the simple reason that the proper antigen is not available for elicitation of the antigen-antibody reaction; the necessary antigen may be a secondary exogenous or even an endogenous allergen. This problem is encountered chiefly in cases of drug hypersensitiveness, but also in numerous cases of urticaria and angioneurotic edema.

DIAGNOSIS OF ALLERGIC DISEASES

QUITE frequently the diagnosis of a given disease as allergic cannot rest on skin testing alone, no matter how elaborate or extensive it may be. This also applies as regards the identification of the causative allergen. Nor do we possess a single general method for determining whether there is an allergic tendency or an already existing allergic state. Futile attempts have been made (employing human dander, peptone, or histamine) to establish a simple method for this purpose.

In performing tests, the specific allergen should preferably be applied to the shock organ. This is especially important in all cases in which there is a localized hypersensitiveness of the mucosa of the eyes, nose, bronchi, or other organs, for in such cases skin tests are often negative. Moreover, the effort to identify the allergen must be conducted according to the nature of the shock tissue involved. Thus, it will differ in dermatitis as compared with urticaria, in light dermatosis as compared with lichen urticatus, and in pollinosis as compared with asthma. Accordingly, the choice of the type of test must take into consideration whether in a given case the epithelium, mucosa, vessels, or other tissue is the primary shock tissue (see Table 4, p. 39). Furthermore, the nature of the suspected allergen (physical agent, chemical substance, or light) must be borne in mind.

It must be admitted that we are today unable to find the allergen in a great many cases. This may be due to the fact that frequently the tests are not performed on the shock organ itself but only on the skin. Moreover, we are not always able to test the shock organ, thus, for example, we do not as yet possess any method for demonstrating hypersensitiveness restricted to the blood vessels of the brain in migraine. In addition, it is often impossible to isolate the causative allergen chemically or biologically, since it is frequently a secondary or endogenous one. Finally, failure to identify the allergen may be attributable to the fact that our search is often undertaken in too routine a manner.

One point must constantly be borne in mind: a substance can be definitely considered as the causative agent in a given case only when avoidance of contact with this substance is followed by disappearance or definite subsidence of the allergic symptoms (avoidance, elimination or withdrawal test), and when, on the other hand, the allergic manifestations are elicited or definitely exacerbated by renewed exposure to or administration of the allergen by mouth, by inhalation, by cutaneous application, or by injection (exposure or re-exposure test). Unfortunately, this clear cut and drastic proof cannot always be obtained, and we must often content ourselves, therefore, with the indirect proof provided by positive skin and mucous membrane tests. The usefulness of these latter tests despite their various liabilities of error, will be appraised below.

The clinical tests include the skin and mucous membrane tests, the diet tests, the environmental avoidance and exposure tests, and the leucopenic index. These will be considered in order, following a brief discussion of the technic of history taking.

A HISTORY

Before any testing can be intelligently performed, a systematic and well organized history must be taken. In order to assure against overlooking any important points, it is advisable to make use of a printed questionnaire (forms used by the authors in the common allergic diseases will be found in the Appendix). Such questionnaires are of course intended to serve merely as a framework for more intensive investigation of the case. The general line of questioning is naturally determined by the clinical picture presented by the allergic disease. Information regarding the precise relationship of the symptoms to the time of day, season of the year, weather conditions, changes in locale and residence, diet, contact with animals, furniture, and bedding, the taking of drugs, the use of cosmetics, the onset of associated allergic and non-allergic complaints and diseases, and a host

of other factors may suggest the most fruitful lines for further investigation and questioning. Careful inquiry must be made as the patient's occupation, environment, habits, activities, and hobbies. The search must be directed as much as possible predisposing as to eliciting factors. Painsstaking questioning—detective work, of a sort—will often yield valuable clues or hints as to the identity of the causative agent, and these indications can then be confirmed by appropriate tests with the suspected allergen. A positive family history is frequently of value. It is often necessary to have the patient's environment inspected by a physician or at least by a trained social worker. It is also very helpful to have the patient write down a detailed account of his daily routine. The patient can be of inestimable help to the physician if he can be made to think along the proper lines.

It will be seen that history-taking in allergy is time-consuming and detailed. Indeed, it often requires more than one interview to complete the necessary information, the patient meanwhile being instructed as to what possible relationships he should look for, and being generally educated regarding allergic mechanisms. Swineford and Weaver⁶⁷ have re-emphasized the importance of a careful and punctilious history, with the questions couched in terms entirely familiar to the patient, and avoiding vague and too inclusive queries. The purpose and approach of an allergy history differ greatly from the usual medical history, partly in that the diagnosis is usually easily arrived at, but chiefly in the placing of the major stress on the recognition of potential offenders. Swineford and Mason's findings in 200 allergic histories correlated with the skin tests show once again that the function of the latter is primarily corroborative, and that they may, in some cases, even be omitted.

B SKIN TESTS

For years there has been a lively controversy as to whether the scratch or the intracutaneous technic* is the more reliable. The

consensus now is that, while no method is entirely accurate, it is best to use scratch tests first, and to follow these up with intradermal tests only with substances that have given negative results but are nevertheless suspected on clinical grounds.

The scratch test is less sensitive than the intradermal test but far more specific. Further advantages inherent in the scratch method are: less danger of constitutional reactions; the elimination of possible syringe contamination, a simpler technic; a minimum of discomfort for the patient from the procedure and from possible positive reactions, and, finally, the considerably lower cost in materials employed. However, if only scratch tests are done, it will not be possible to discover the cause of the allergic disease in many patients who are clinically sensitive but whose sensitivity is of such degree that they will fail to react to tests done by this method. The intracutaneous tests are unquestionably far more sensitive, but, as mentioned, this is at the expense of specificity. Furthermore, the intradermal tests involve a number of possible sources of error (see p. 169): the results—whether positive or negative—cannot, therefore, be accepted as specifically positive or negative without additional evidence. This is one of the important reasons why this method has not become popular, and why it is useful only in the hands of specially trained and experienced physicians who have considerable control material at their disposal. Despite all the possible sources of error, however, the intracutaneous test method is an important and often indispensable procedure. It has the added advantage of permitting "titration" of the degree of sensitivity, by determining the least concentration of the allergen capable of eliciting a demonstrable reaction. It must be pointed out, however, that the cutaneous sensitivity so determined need not parallel the severity of clinical symptoms. In summary, these tests, under suitable conditions, are permissible with substances that have failed to produce reactions by the scratch technic. The claim that if all the scratch tests are negative any number of intradermal tests may be performed with safety is not entirely true, as pointed out by M. Walzer,⁶⁸ and

⁶⁷ SWINEFORD, O., JR., and WEAVER, W. M. *Ann. Int. Med.* 29: 293, 1944.

* To avoid confusion, the elementary fact is here reiterated that the patch test is capable of demonstrating only epidermal sensitivity, and can by no means be used in place of either of the above tests.

⁶⁸ WALZER, M. *J. Pediat.* 21: 132, 1942.

no more than 15 to 20 intradermal tests should be done at one time. They may be undertaken without previous scratch testing with bacteria, yeast and molds since these agents do not cause severe general manifestations.

According to A. H. Fineman the intradermal tests are about one hundred times more sensitive than the scratch tests. In other words a dilution of 1:50 for scratch tests is approximately equivalent to a 1:5000 dilution for intracutaneous testing. Vaughan recommends that when a cutaneous test with a 1:50 dilution is negative the intradermal method should be tried with a 1:500 dilution—that is to say with a dilution that is only ten times weaker—while dilutions of 1:1000 are to be employed only when dealing with notoriously strong allergens (e.g. cottonseed flaxseed horse dander and pollen extracts).

Other authorities on the basis of clinical experience have specified the optimal concentrations of each extract to be used in scratch and intracutaneous testing in terms of weight volume dilution, nitrogen content or protein nitrogen content. However it has long been recognized that none of these methods of standardization accurately reflect either the potency or the specificity of an extract. Moreover non specific reactions may be produced by the trauma of the test by excessive concentration of the extract by primarily urticarogenic substances and by the glycerine or histamine content of the extracts further confusing the results. Efron et al.⁶⁵ have therefore developed a biologic method of standardization. In brief this consists of the testing of each extract on adequate groups of allergic patients particularly those known to be sensitive to the substance in question and of non allergic subjects. Statistical methods may then be employed to determine the diagnostic reliability of the extract and are fully outlined in the articles by these authors. Biologic standardization is required for the quantitative estimation of certain attributes of insulin, liver extract and certain endocrine and vitamin preparations and may be as

logically applied to allergic extracts. On the basis of observations on freshly prepared extracts of fruits and vegetables and the rapidity of their deterioration Tuft, Blumstein and Wenger⁶⁶ also recommend the biologic assay method of standardization as well as the elimination from the testing list of certain extracts which are either inert or give reactions of questionable value. Although not strictly pertinent to the present discussion it should be noted that biologic standardization is also applicable to patch test material particularly plant extractives which vary in antigenicity from batch to batch and in which no physical or chemical unit is an accurate index of specific potency. Thus Stevens⁶⁷ has suggested biologic assay of poison ivy extracts.

Skin tests are usually performed on the flexor surface of the forearms on the outer surface of the upper arms and on the back. In controlled tests Ballesterro and Mom⁶⁸ found the sites of greatest cutaneous reactivity to scratch, intracutaneous and patch tests to be a band zone on the anterior surface and internal edges of the arms and forearms corresponding to the peripheral distribution of the fifth and sixth cervical and first dorsal spinal nerve roots. All three types of skin tests showed parallel variations as regards cutaneous activity except on the back where scratch tests were hardly noticeable although the others reacted and on the abdomen in the zone innervated by the eighth to tenth dorsal segments where the results of intradermal tests were comparable to those on the arms. Seborrheic hairy and thick skin areas showed less reactivity than dry glabrous thin ones. Reactivity decreases on the mid line of the body.

Another question to be considered is: Should tests be made with single extracts or with groups? Group testing means that tests are made with mixtures of related allergens thus obviating the necessity of making a large number of individual tests. For example a mixed extract of epithelial substances might contain extracts of horse, dog and cat hair as well as of horse, dog and cat dander.

* EFRON B. G. J. Allergy 14: 49, 1942; EFRON B. G. BOATNER C. H. PARST M. R. and FLEHMAN J. K. Biologic Assay in Allergy. Lett. Nat. Co. Club of Allergy Sec. 43: 42, 50, 66, 81, 1941; EFRON B. G. and BOATNER C. H. J. Invest. Dermat. 5: 49, 1942; PARST M. R. BOATNER C. H. and EFRON B. G. New Orleans M. & S. J. 92: 579, 1941.

* TUFT L. BLUMSTEIN G. I. and WENGER L. J. J. Allergy 16: 92, 1941.

† STEVENS F. A. J. Allergy 17: 912, 1941.

‡ BALLESTERRO L. H. and MOM A. M. Rev. argent. dermatol. 1: 26, 1103, 1942.

The present tendency is to disapprove of group testing. This is because the mixing naturally results in lower concentrations of each of the component substances than there would be if the constituents were used separately. Furthermore, as shown by Berger and Hansen, the group of extracts may elicit a positive reaction, while the components—used in separate tests—give negative results; and, conversely, it sometimes, though rarely, happens that some of the components elicit positive reactions singly while there is no reaction to tests with the group as a whole. Hence, Berger and Hansen conclude that if only group testing is performed, important allergizations may sometimes escape attention.

The allergic skin reactions manifest themselves in three different forms: (1) an immediate-urticarial reaction, due principally to exudative vascular changes, (2) a delayed-papular reaction, due to infiltration of the cutis and usually consisting of cellular vascular changes; (3) a delayed eczematous reaction, consisting of epithelial changes. The last is seen only after patch testing.

1. SCRATCH TEST

The cutaneous test was first employed in 1873 by Blackley to determine the presence of hay fever. This technic, however, seems subsequently to have fallen into oblivion. It not until 1907 that it was again heard of in the literature, for it was then that von Pirquet reported his technic of cutaneous testing with tuberculin. In 1917, Walker employed this method for testing for allergic conditions in general.

TECHNIC. A number of scratches about 0.5 cm ($\frac{1}{2}$ inch) in length are made on the slightly stretched skin of the forearm or of the back, after the surface has been cleansed with sterile water or physiologic salt solution. Alcohol or ether may not be used, as these may possibly influence the reaction. The skin must be thoroughly dry before scarification. The scratches must be tears rather than cuts. They are best made with a small cataract knife or with a common sewing needle in a suitable holder (Fig. 43). A circular scarifier is recommended for use on children. The instrument should just barely penetrate the epidermis, blood should not be drawn. Each of the scratches is covered with 1 drop of N/20 sodium hy droxide. Into this drop one then mixes as much of the protein as will cover the flat end of a toothpick (which is to be thrown away). This solution must not be permitted to dry; if necessary,

more of the sodium hy droxide is added. The materials necessary for scratch testing are provided in convenient outfits (Fig. 44) by a number of commercial houses. When liquid extracts are employed, they should be kept in small bottles with corks provided with platinum loops. This loop is used to apply the extract directly to the skin. The loop is then flamed. If the cork is provided with a rod, the apex of the drop is allowed to come in contact with the skin, the rod itself must not touch the skin. The same instructions apply to the use of dropper applicators consisting of rubber-bulb stoppers and capillary glass tubing. For those doing tests relatively infrequently, extracts are also packaged in single test sealed glass capillary tubes, the contents of which are expressed after the ends are broken off. The control test consists of a scratch plus a drop of N/20 sodium hy droxide alone. This test reveals the patient's reaction to the trauma and to the sodium hy droxide. From ten to twenty scratches may be made at one sitting. The scarifications are to be made about 2.5 cm (1 inch) from one another. They should be carefully planned and arranged, in order to avoid

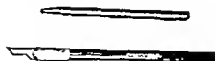


FIG. 43 INSTRUMENTS FOR SCRATCH TESTING
Scarifier, borer

possible confusion in reading the results. A 2 per cent alcoholic solution of eosin or a black eyebrow pencil is used for skin marking.

In order to avoid some of the disadvantages of the scratch method, particularly the difficulty of achieving the proper depth of lacerating the skin, several alternative technics have been utilized. The pressure puncture method is performed much like the multiple pressure method in smallpox vaccination: one to three punctures are made through a droplet of the liquid allergen, carrying it directly into the deeper layers on the skin. This technic is particularly suitable for children (Stoesser²²), since it is less painful and eliminates the necessity of the patient's remaining still in order to keep the drops in place. Levinton²³ has adapted a small portable motor-driven dental drill, gentle application of which peels away the epidermal cells from a small area and, with proper application, to a constant depth rapidly and almost painlessly. The allergen is then applied to this superficial abrasion. Vollmer, Hyslop, and Lomant²⁴ devised a match like apparatus the head of which consists of fine pumice powder held in place by a cement substance, impregnated with glycerinated extracts of various allergens, such as pollen, ornitho, house dust, or egg white. Two or three turning movements of the "match" with the head gently pressed

²² STOESSER, A. V. *Journal Lancet* 64, 145, 1944

²³ LEVINTON, J. J. *Allergy* 15: 300, 1944

²⁴ VOLLMER, H., HYSLOP, H. W., and LOMANT, H. V. *J. Pediat.* 21: 747, 1942

against the stretched skin accomplishes a painless abrasion of the stratum corneum brings the test substance into contact with the reactive cell layers and is not alarming to children. Results with tuberculin and Schick testing are less satisfactory with this method. All these reactions are interpreted similarly to the usual scratch test. It should also be noted that the percutaneous and electrophoretic tests (see below) while differing in that the antigen is applied to the intact

all test sites including the control. Feinberg and Friedlaender⁶⁸² recently suggested that this difficulty may be circumvented by means of a new synthetic histamine antagonist β -dimethylaminoethyl benzhydryl ether hydrochloride. When patients were given 50 mg of benadryl five hours, three hours and one

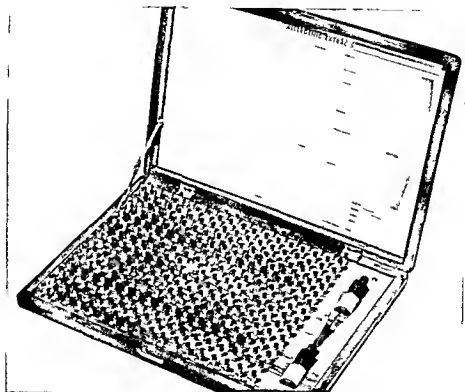


FIG. 44. DIAGNOSTIC KIT FOR SCRATCH TESTING
(Courtesy E. R. Squibb and Sons)

skin achieve a similar purpose in carrying the allergen through the stratum corneum and to the deeper layers.

A typical positive reaction presents an urticarial wheal with surrounding erythema (Fig. 45); it usually appears within ten to twenty minutes. An area of swelling and erythema less than 5 mm in diameter is to be interpreted as a negative reaction. Obviously the result of the control test indicating the response to the trauma must always be taken into consideration (Table 18, p. 166). It is apparent that the presence of dermographism will interfere greatly with the reading of the reactions and indeed make it impossible since a pseudoreaction will appear at

hour before testing there was either complete or partial inhibition of the dermographic whealing and the usual cutaneous reactions to allergens were demonstrated.

Specific lymphangitis is very rarely seen. Occasionally delayed reactions to protein or pollen extracts appear; these reactions are completely ignored by some authors while others consider them of some significance. The question as to the extent to which such delayed reactions are to be considered specific is still unsettled. It must be noted that these last remarks do not apply to tests with tu-

⁶⁸² FEINBERG, S. M. and FRIEDLAENDER, S. *J. Allergy* 16: 290, 1941.

berculin, trichophytin, and bacterial allergens, since these agents almost invariably elicit delayed reactions.

In the case of patients known to be extremely hypersensitive (e.g., to horse serum or egg white) it is advisable to begin cautiously, using

Brown), chocolate (E. A. Socola), brazil nut (J. Fries), and yellow jacket extract (G. W. Owen). They may occur when scratch tests are made with drugs, even if the tests are negative (Walzer⁶⁷). According to Vaughan, three deaths have been reported in the entire

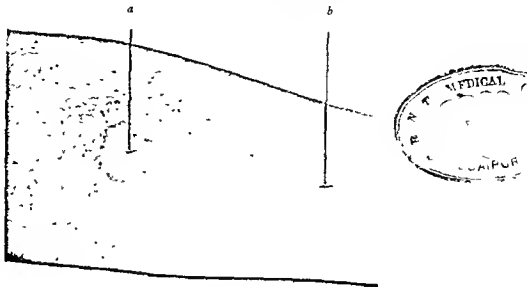


FIG. 45. SCRATCH TEST

a = positive reaction b = control

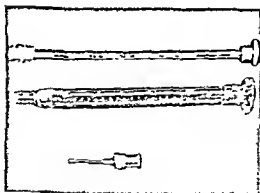


FIG. 46. SYRINGE FOR ALLERGY TESTING AND TREATMENT

Barrel graduated to 0.01 cc., metal asbestos-wrapped plunger, and 27-gauge needle, $\frac{1}{2}$ inch in length

tenfold to hundredfold dilutions, and to employ stronger concentrations only when the weaker doses have failed to elicit a reaction. Severe constitutional reactions following cutaneous testing have, on very rare occasions, been observed (Rosh and Schiff, Kolmer, P. Vallery-Radot and Haguénau). More recently, generalized reactions have been observed from scratch tests with pollen (A. S.

literature—two from testing with buckwheat, the other with egg

2. INTRACUTANEOUS TEST

The intracutaneous or intradermal test with tuberculin was simultaneously reported, in 1908, by Mendel and by Mantoux. In 1912 O. Schloss employed this method for allergic skin testing.

TECHNIC The patient is seated sideways on a chair, with one arm resting on the padded arm of the chair, if many tests are to be performed, the patient lies prone on an examining table. The skin sites are cleansed superficially with cotton moistened with 70 per cent alcohol or acetone. A 27 gauge rustless needle, 1 cm. (3/8 inch) in length fixed on a tuberculin syringe,* is inserted with the bevel up and almost parallel with the surface of the skin. The bevel should be visible through the epidermis. The Tubex outfit made by Wyeth (Fig. 47) may also be used and is a convenient, specific, and rather safe method, as determined by O. Belmont in the Allergy Department of the senior author. In

* Since the tuberculin syringe, usually employed are provided with both metric and apothecary graduation, there is a possibility of confusion and of dangerous mistakes. It is best therefore to employ for this purpose only syringes graduated to 0.01 cc. (Fig. 46).

either case a quantity of 0.01 or 0.02 cc of extract suffices to produce a visible wheal. Quantities of more than 0.02 cc of extract may cause nonspecific irritation (pseudoreactions). When on clinical grounds a strong reaction may be expected the volar surface of the forearm should be used. The sites for testing should be at least 2.5 cm (1 inch) apart laterally and 5 cm (2 inches) apart longitudinally. No more than ten tests should be made at one time and these should be of different allergic groups. One should not for example test simultaneously with all the pollen extracts which may lead to a summation of the effects and possibly to a constitutional reaction. If these tests

between two kinds of reactions—the immediate urticarial and the delayed inflammatory.

A reaction is considered immediate when it appears within twenty minutes and presents an urticaria like wheal or irregular shape surrounded by an erythematous halo (Fig. 48). In cases of extremely marked hypersensitivity pseudopod like branches extend from the wheal (Fig. 49).

All data as to the size as well as the time of appearance and disappearance of the reaction

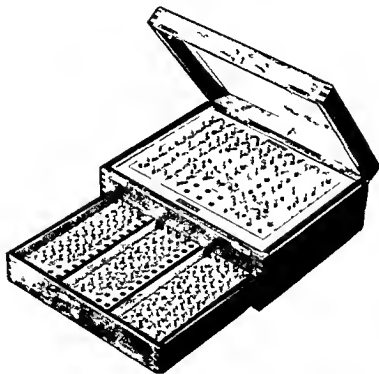


FIG. 47. DIAGNOSTIC OUTFIT FOR INTRACUTANEOUS TESTING WITH THE TUBEX METHOD

(Courtesy Wyeth Inc.)

elicit only a mild response ten additional tests may be made. It is usually a good policy to make no more than twenty tests at one sitting.

Cocaine solution, physiological saline solution, or other diluents are used for the control injections depending on which is employed for diluting the extracts. For testing children under 2 years of age it is advisable to use extracts of about one-tenth the strength employed for adults.

When is a reaction to be interpreted as specifically positive? Before attempting to answer this question we must differentiate

serve merely as an approximate standard for as will be explained in greater detail below the reaction is dependent upon a great variety of circumstances. Comparison with the control sites is the only criterion. There seems to be some question as to whether the wheal or the erythema is to be considered the more significant in evaluating the reaction. In agreement with the majority of authors we consider the wheal to be of far greater importance for the surrounding erythema is

produced by a reflex mechanism, since it does not occur in the skin of an area under spinal anesthesia (von Groer), or in a limb paralyzed by peripheral nervous disease (Ebbecke).



FIG. 48 INTRACUTANEOUS TEST IMMEDIATE REACTION
(TO RABBIT SERUM)

zone of vasoconstriction (FIG. 50). It usually appears in from twelve to eighteen hours, reaches its maximum intensity in twenty-four hours, and may persist for two or three days.

What is the relation between the two types of skin reaction—the immediate-urticarial and the delayed-inflammatory or “tuberculin-type”? What is their significance? In the literature the immediate reactions have been referred to as “anaphylactic” or “atopic,” while the delayed-inflammatory reactions have been called “allergic.” There are distinct clinical and histologic differences between the two forms of reaction; but the significance of these differences is not, as yet, well understood. There is some evidence suggesting that the two reactions may represent merely two phases of the immune process. Thus, Dienes⁵³ showed that when guinea pigs were given daily intracutaneous injections of foreign serum or of egg white for three or four days, the response consisted of a definite red inflammatory reaction appearing twenty-four hours after

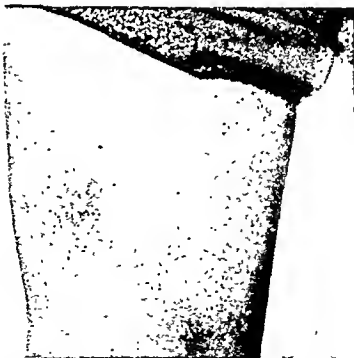


FIG. 49 POSITIVE INTRACUTANEOUS REACTION WITH PSEUDOPODIA

A delayed reaction is characterized by a rather intensive erythematous infiltration (papule) and by a large or small inflammatory halo that is sometimes surrounded by a white

the last injection. After some eight to ten days of this treatment, however, the responses changed to the immediate-urticarial type,

⁵³ DIENES, L. *J. Immunol.* 35: 153, 1929; 20: 333, 1931.

and were accompanied by the development of circulating antibodies in the animal. Simon and Rackemann⁶⁸⁴, Jones and Mote⁶⁸⁵ and Tezner⁶⁸⁶ made similar observations on human beings who had been sensitized with guinea pig serum. The immediate type of reaction is associated with antibodies that can passively transfer the hypersensitiveness to a normal recipient. While these authors (with the exception of Tezner) believe that the two forms of reaction represent nothing more than two different phases of the responses of normal animals and man to repeated intracutaneous injections, Sulzberger⁶⁸⁷ is of the opinion that these different reaction types are



FIG. 80. INTRACUTANEOUS TEST. DELAYED REACTION (TO TUBERCULIN 1:100,000). Lower marking indicates control site.

separate and distinct and apparently due to entirely different forms of skin sensitivity. He also stresses the differences in their histology: the characteristic lesion of the immediate urticarial reaction is an extravasation of fluid and of some cells through the walls of the damaged vessels; the delayed tuberculin type, for the first ten days, shows a uniform response consisting of a focal perivascular cellular infiltrate composed chiefly

of small lymphocytes; the blood vessels are dilated and contain polymorphonuclear leukocytes (Pascher, Sulzberger and Satenstein⁶⁸⁸). In some specimens taken after 48 hours a proliferation of fibroblasts and histiocytes are noted. However, two to five weeks after the injection of old tuberculin Koch or tuberculin PPD, tubercles and tubercloid structures with an increasing number of epithelioid cells are observed.

According to Tezner⁶⁸⁶ the delayed reaction is a sign of experimental parenteral sensitization, while the immediate reaction is encountered only in natural sensitizations. This view is not tenable—if for no other reason than that there is no fundamental difference between natural and experimental allergization.

Vaughan⁶⁸⁹ holds that delayed reactions appear when the body has been chronically exposed to the allergen—especially therefore in bacterial allergies. On the other hand, Stevens and Jordan⁶⁹⁰ showed that the type of response depended largely on whether injections were made with either living or whole killed organisms or with extracted materials (such as bacterial nucleoprotein); in the former case there were immediate urticarial reactions, in the latter delayed reactions. However, Lewis and Hopper⁶⁹¹ and Marcussen⁶⁹² found that trichophyton not infrequently produced an immediate urticarial reaction in patients with trichophytosis, provided the site is inspected at the end of ten or twenty minutes and in some instances circulating antibodies were demonstrable by positive passive transfer tests. McEwen and Swift⁶⁹³ demonstrated that animals treated intravenously with bacterial substances reach a high serum antibody titer, while the extent of the cutaneous hypersensitiveness remains moderate and of the immediate urticarial type. In animals treated intracutaneously, however, scarcely any circulating antibodies were observed to develop, while cutaneous tests elicited strongly positive reactions of the delayed tuberculin type. Furthermore, these authors as well

⁶⁸⁴ SIMON F. A. and RACKEMANN F. M. *J. Allergy* 5: 439, 1934.

⁶⁸⁵ JONES T. D. and MOTE J. R. *New England J. Med.* 210: 120, 1934.

⁶⁸⁶ TEZNER O. *Klin. Wochenschr.* 14: 539, 92. *Zeitschr. f. klin. Med.* 145: 86, 1935.

⁶⁸⁷ SULZBERGER M. B. *J. Allergy* 38: 1936.

⁶⁸⁸ PASCHER F., SULZBERGER M. B. and SATENSTEIN D. I. *J. Immunol.* 46: 195, 1943.

⁶⁸⁹ VAUGHAN W. T. *J. Lab. & Clin. Med.* 14: 433, 1929.

⁶⁹⁰ STEVENS F. A. and JORDAN L. *J. Immunol.* 31: 51, 1936.

⁶⁹¹ LEWIS G. M. and HOPPER M. E. *An Introduction to Medical Mycology*, 2d ed., Chicago, 1934, *Bl. Pub.* 1943.

⁶⁹² MARCUSSEN P. V. *A. Ch. Dermat. & Syph.* 36: 494, 1937.

⁶⁹³ MCEWEN C. and SWIFT H. F. *J. Exper. Med.* 62: 573, 1933.

as Stevens and Jordani, found that when formed elements were used for preparation, more circulating antibodies (precipitins) developed and the cutaneous reactions were of the immediate type, while protein fractions, on the other hand, elicited delayed reactions.

All this seems to be somewhat confused. Our own opinion is that the immediate and delayed reactions are differentiated by the fact that the former occurs when circulating antibodies have been formed in the organism, as evidenced by a positive passive transfer with blood serum (Prausnitz-Kuestner test). The delayed reaction, on the other hand, is an expression of an immune process in the course of which cellular antibodies are formed, as shown by passive transfer with blister fluid (Urbach-Koenigstein test). This concept explains why under certain circumstances the immediate or the delayed or both reactions will be encountered. Hence, it is essential that readings of the tests should be made after twenty minutes and then again after twenty-four and forty-eight hours.

The strength or intensity of a reaction depends upon various factors: (1) the concentration of the allergen (FIG. 51), (2) the site of injection—the tendency to wheal formation is strongest on the flexor and extensor surfaces of the arms and then, in order, on the back, (3) the patient's reaction capacity, (4) the quantity of circulating and cellular antibodies.

A reaction can be recorded in various ways: namely: by measuring the diameter of the wheal; by tracing the reaction and weighing the paper representing it, or by Abramson and Gorin's⁵⁹¹ contour gauge, which measures and records the rate of increase of both the height and the breadth of wheals.

Intracutaneous tests should be read after twenty minutes. The greatest care must be exercised in interpreting reactions. One should consider a reaction positive only when the wheal and erythema are larger than they are in the control. In other words, whatever wheal and erythema are seen at the control sites must be subtracted, so to speak, from the reaction at the test sites. With due regard to this consideration, a positive reaction may be said to consist of a wheal, with or without

pseudopodia and itching, usually surrounded by a zone of erythema.

The positive reactions are conventionally recorded as one to four plus, according to their size, whealing, and pseudopodia. The grading depends on whether the reaction is immediate or delayed, as shown in Table 18. A failure to react, or a reaction of the same

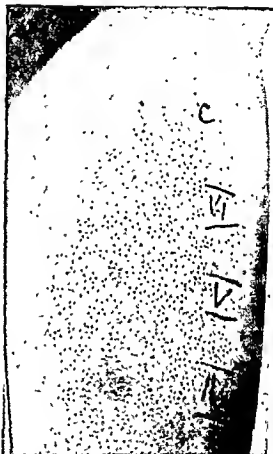


FIG. 51 INTRACUTANEOUS TESTING WITH INCREASING CONCENTRATIONS

C = control negative V1 = old tuberculin, 1:1,000,000, negative V = old tuberculin, 1:100,000, positive IV = old tuberculin, 1:10,000, strongly positive

size as in the control, is called negative and recorded with a zero (0), reactions only slightly stronger than those in the control sites, by "plus-minus" (\pm).

The value of intracutaneous tests depends upon the correctness of the technic, the use of proper extracts, the reaction capacity of the patient, and, above all, the critical evaluation of the reaction.

To prevent nonspecific reactions in the course of intracutaneous testing it is advisable to inject no more than 0.01 to 0.02 cc of the extract. For, although Coca and others have stressed the point it is not yet generally appreciated that, in the intracutaneous technique the quantity of the injected fluid is to a certain extent, of greater importance than the concentration of the allergen. Furthermore, and not infrequently, the degree of specific hypersensitiveness is incredibly high. We would call attention to the case of a woman hypersensitive to tuberculin (Fig. 229, p. 461) who responded with a definite skin reaction to a dilution as high as 1:1,000,000,000. Schmidt reported a case in which the patient reacted distinctly to a 1:10,000,000,000 solution of a

lem in the following manner. Each protein group has its own similarly numbered syringes and needles; these are placed in perforated glass containers in such a manner that they are sterilized by live steam, which is allowed to enter but not to leave (condensation takes place in a special device at the top of each container).

As regards the stability of intracutaneous test extracts they do not retain their full strength for more than a few months. Extracts of fruits are particularly labile, according to Tuft and Blumstein.⁶⁹ The demonstrable allergenic potency of the juice of fresh or fast frozen fruit was largely lost in the first 24 hours, presumably due to the action of an enzyme and completely within 3 to 4 days,

TABLE 18—Reading of Skin Tests

SCRATCH AND IMMEDIATE INTRACUTANEOUS TESTS (With Proteins, Pollens, Dust)

- 0 = reaction of same size as in control
 + = reaction twice as large as in control
 ++ = wheal 15-25 mm in diameter
 +++ = large wheal (exceeding 25 mm in diameter) without definite pseudopodia
 ++++ = large reaction with definite pseudopodia

DELAYED INTRACUTANEOUS TESTS (With Tuberculin, Vaccines, Bacterial Products)

- 0 = reaction of same size as in control
 ± = slight erythema approximately 5 mm in diameter
 + = infiltration and erythema 5-10 mm in diameter
 ++ = infiltration and erythema 10-15 mm in diameter
 +++ = infiltration and erythema 15-20 mm in diameter
 ++++ = infiltration and erythema exceeding 20 mm in diameter
-

feather extract. When such a highly hypersensitive individual is to be tested, extraordinary care must be taken. Thus, if the patient is known to be extremely hypersensitive to egg albumin, for example, and if an intracutaneous test (e.g., with milk) is made with a syringe that has previously been used for testing with egg, the subsequent positive reaction may well be due to residual traces of egg, and not to milk.

In dealing with such highly hypersensitive cases, it is advisable to use a separate syringe for each of the different proteins. It has even been recommended that each syringe be cleansed and boiled in a separate container. Urbach⁶⁹ has attempted to solve this prob-

lem by materially reducing by Seitz filtration, and was altered or destroyed by heat during canning and stewing processes. Alkalinization prolonged the activity for a limited time, and lyophilization of the fresh juice for at least 6 months, although deterioration was rapid after the lyophile was redissolved. Tests with concentrated stock extracts were negative. These observations probably account for the inadequacy of tests for fruits and possibly other foods.

Moreover, particularly in connection with food sensitivity, skin test reactions often cannot be elicited because the allergen is not the ingested protein *per se*, but a decomposition

⁶⁹ TUFT, L. and BLUMSTEIN, G. I. *J. Allergy* 13: 574, 1942; 15: 346, 1944.

product formed from it in the course of digestion—a secondary allergen. This is clearly shown by the observations of Blamoutier¹⁰⁵⁶ in the case of a patient who invariably developed generalized urticaria with angioneurotic edema each time he ate lamb or mutton but who failed to react to tests with these foods. However, when samples of the meat were incubated with both gastric and duodenal juices (but not with either one alone), positive skin reactions were obtained, and the Prausnitz-Kuestner passive transfer test was also positive. This approach not only confirms the existence of secondary allergens, but indicates a method whereby, in appropriate cases, such allergens can be obtained for test purposes.

Furthermore, it is very often imperative to test the patient with substances taken from his own environment: a purchased dust extract, for example, need not necessarily contain the guilty ingredient of the patient's own house dust, nor will a commercial feather extract contain the decomposition products of parasites, which may actually be the offender in a given case. Quite often, therefore, it is necessary to have "autogenous" extracts individually prepared from materials provided by the patient.

With reference to the reaction capacity, the following points are to be observed. When a patient's skin reacts to all extracts and controls (FIG. 52), the test must be considered worthless, for the patient's cutis is nonspecifically sensitive. Before this conclusion is drawn, however, it must be determined whether these reactions are due to the diluent or to the physical irritation caused by the needle; a blank needle prick will serve as control. But when the patient responds with reactions to a limited number of allergens (FIG. 53), the tests may be a diagnostic aid, provided the other conditions (see above) appear to be fulfilled. It must be stressed, however, that the intensity of the reaction on intracutaneous testing is by no means parallel to the severity of the symptoms.

As to the critical evaluation of reactions, it must be emphatically pointed out that positive skin tests may reveal past, present, or future (potential) sensitiveness, or, more explicitly, a positive skin reaction alone gives

nothing more than evidence of exposure and of sensitization that is sometimes only latent. The skin reaction should always be correlated with the clinical history and with tests by appropriate methods, such as avoidance and exposure.

Concerning the incidence of positive reactions, it is necessary to consider this separately in respect to clinically allergic and nonallergic individuals. In the latter group, special attention has been paid to the effect of occupational and environmental allergens.

Baagøe⁶⁹⁷ examined 121 cases of asthma and found that 75 per cent gave positive skin



FIG. 52 POSITIVE INTRACUTANEOUS TESTS WITHOUT DIAGNOSTIC SIGNIFICANCE

If all or most of skin sites respond to various allergen reactions must be considered nonspecific and are of no aid in establishing etiologic diagnosis. In this subject, even saline control (site 6) produced small wheal.

reactions. In only 33 of 88 cases, however, was he able to demonstrate clinical hypersensitiveness to those substances to which the patient reacted, and in only 18 cases did elimination of these allergens lead to a cure or to considerable improvement of the asthmatic condition. Withers⁶⁹⁹ found that of 91 patients with clinical hypersensitiveness, only one-half had accompanying positive cutaneous reactions. On the other hand, of 65 patients showing no clinical reactions, 31 had positive cutaneous reactions—again nearly one-half. Rinke⁷⁰⁷ states that in large groups of patients

⁶⁹⁷ BAAGØE K. H. *Klin. Wchnsch.* 7: 60, 1924

⁶⁹⁹ WITHERS O. R. *J. Allergy* 10: 105, 1949

at least 20 per cent of the foods actually the cause of allergic symptoms will cause skin reactions while positive tests are associated with clinical reactions after the ingestion of the food about 40 per cent of the time. The fact that some foods which give comparatively weak reactions are often more important clinically than those which produce strong reactions was again pointed out by Stoesser⁵⁹ with pertinent examples.

The frequency with which positive reactions are elicited with particular extracts varies widely in different allergic diseases with the nature of the allergens and in the hands of

and hence their greatest value in hay fever followed by allergic rhinopathy and exogenous allergic asthma. They are of limited value in infantile dermatitis neurodermatitis and migraine and of little or no value in food allergy urticaria angioneurotic edema and gastro intestinal allergy.

Healthy individuals—i.e. persons who give no evidence of being allergic—rarely react to scratch tests but frequently respond with positive reactions to intracutaneous testing. Rackemann and Simon⁶⁰ noted positive reactions in 50 per cent and Grow and Herman⁵⁵ in 55 per cent of 150 normal persons. Ber

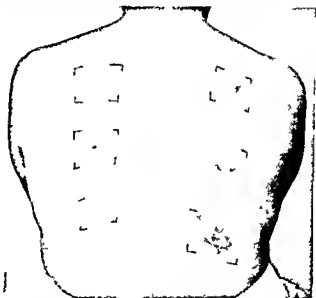


FIG. 53 INTRACUTANEOUS TESTS OF DIAGNOSTIC SIGNIFICANCE
Three positive and three negative reactions

various investigators. Inhalants are the least likely to give rise to misleading reactions and this is probably particularly true of pollens. Although positive reactions from dust, animal emanations, feathers and cottonseed are usually of value, those to flaxseed, tobacco and pyrethrum are not always indicative of the true state of sensitization of the patient. And as already indicated, tests with foods other than milk, egg, cereals, fish and chocolate are apt to be erroneous. (As a consequence, positive skin reactions to foods should never constitute the basis for permanent removal from the diet.) As a broad generalization, skin tests have their greatest accuracy

ger⁶¹ tested 207 healthy persons intracutaneously with forty to fifty different allergens and found that 56 per cent of these individuals responded with some reaction, 36 per cent gave moderately strong positive responses to from one to three allergens and 10 per cent similarly to four or more allergens and very strong positive reactions were shown by 7 per cent to one allergen and by 3 per cent to several allergens.

Salen and Juhlin Dannfelt⁵⁴ examined 432 persons who gave no clinical signs of allergy and who belonged to different occupational

⁵⁹ BERGER, W. *Wochenw. Wechschr.* 43: 513, 1930.

groups, and found that intracutaneous tests elicited individual positive reactions correlated closely with the respective occupations. Thus, bakers reacted to wheat in 38 per cent of the cases, but not to horse dander, cavalrymen to horse dander (23 per cent) but not to wheat, and so on. The authors interpreted these results as suggesting the presence of latent allergy, since positive cutaneous reactions were elicited only by allergens to which the individuals were regularly exposed. Colmes, Guild, and Rackemann⁷⁰ studied a group of bakers and found that about 40 per cent showed cutaneous sensitiveness, although only one individual had clinical symptoms. Similarly, a higher incidence of reactions to feathers is found in babies sleeping on feathers than among babies not so exposed (Hill, Peck, and Salomon); and a higher incidence of tobacco reactions is present in smokers than in non-smokers (Harkavy, Sulzberger).

As Sulzberger⁴ correctly points out, these statistics seem to answer the important question as to the meaning of these frequently occurring positive reactions without demonstrable clinical symptoms. The answer is that while these reactions are often an expression of a specifically acquired hypersensitiveness, this is quite frequently of such low degree that it does not give rise to clinical symptoms.

It is apparent from the foregoing that in evaluating the results of skin tests performed in an effort to determine the etiology of a patient's disease, it is essential to cultivate a critical attitude. Alvarez⁷¹ states, "It is unfortunate that so many patients [and, we might add, physicians] get the idea that the skin tests are like gospel truth." Black²⁷⁶ emphasizes the fact that skin tests, no matter what method is used, are quite fallible. False positives may be obtained and false negatives are frequent. The worker who depends wholly upon skin reactions to determine the cause of the patient's allergy will frequently have nothing to lean upon. In such circumstances, intelligent application of the other diagnostic measures discussed in this chapter will often elicit the cause of the allergic symptoms.

CAUSES OF "FALSE POSITIVE" REACTIONS

Not infrequently the skin reacts to substances to which the patient is clinically insensitive. These "false positive" reactions may be due to:

(1) Nonspecific hyperreactivity of the capillary system, recognizable by the presence of dermographism. This source of error can be eliminated only by means of the required control with physiologic saline solution.

(2) Nonspecific irritating qualities of the extract, including excessive concentration of the extract. The solution must not only be sterile, of course, but must also be of neutral reaction and isotonic, since free OH or H ions as well as hyper- and hypotonic solutions are capable, in themselves, of eliciting strong nonspecific reactions. The temperature of the injected fluid must be moderate, to obviate the danger of thermal irritation.

(3) Trauma of the injection. There is a type of pseudoreaction resulting from the intradermal injection itself and giving rise immediately to a large wheal with pseudopodia. This occurs when a rather large quantity is injected too superficially and forcibly. This type of reaction can be identified by the following features: marked burning or pain, in excess of the discomfort felt in connection with the other injections, and persisting for a few or even for many hours. It is characteristic that the injected fluid spreads out quickly between the layers of the skin. When such a cause of positivity is suspected, the test must be repeated in another site.

(4) Sensitivity to the preservative (e.g., phenol, merthiolate, glycerin, or quinine) contained in the extract.

(5) Contamination of the syringe by substances remaining from previous testing or treatment. Many allergens form stable films on glass and metal equipment that are not removed by rinsing nor destroyed by the ordinary methods of sterilization (Small and associates⁷⁰²).

(6) Previous oral administration of iodine, especially in tests with tuberculin and lueticin.

(7) Metalallergic influences (see p. 28). Thus, during the hay fever season, the skin of a hay fever patient is likely to be hypersensitive to

⁷⁰ COLMES, A., GUILD, B. T., and RACKEMANN, F. M. *J. Allergy* 4: 579, 1935.

⁷¹ ALVAREZ, W. C. *Nervousness, Indigestion and Pain*. New York: Hoeber, 1943.

⁷⁰² SMALL, W. S., HAWES, R. C., MILLER, H., and PRESS, G. *J. Allergy* 13: 330, 1942.

substances that are at other times without effect, tests should, therefore, always be undertaken during attack free periods. The group of metallergic influences also includes the effect of chronic infections, such as tuberculosis. For example, individuals suffering from superficial fungous infections will usually react negatively to trichophyton, but will exhibit cutaneous reactivity when also suffering from tuberculous infections that lead to positive tuberculin reactions (Peyrer⁷⁰³).

(8) A close immunologic relationship (so called common allergenic grouping), between two or more allergens

(9) Loss of specificity on the part of the organism (as for example, in asthma of long standing)

(10) *Psychic factors*. In order to eliminate such influences as far as possible, it is best not to let the patient know the nature of the material to be injected. The patient's awareness of the identity of the test allergen may possibly tend to influence the reaction in either direction (see p. 76).

In order to determine whether a positive reaction is specific or nonspecific, it is best to use the passive transfer test, by the *Pransmits Kuestner* or the *Urbach Koenigstein* method.

CAUSES OF "FALSE NEGATIVE" REACTIONS

The absence of reaction to intracutaneous testing does not necessarily mean that there is no underlying allergy. Such "false negatives" may be due to

(1) Absence of the allergen in the series used for testing

(2) Use of solutions that are too old or too weak

(3) The difficulty of obtaining effective extracts of some foods, especially fruits and vegetables, due to rapid deterioration from the fresh state and loss of the allergenic principle on standing or processing

(4) The fact that the allergy is caused not by simple exogenous substances per se, but by metabolic products and derivatives formed from them within the organism, and then acting as allergens (secondary allergens)

(5) Hypersensitiveness to substances formed within the organism (endogenous allergens)

(6) The fact that sometimes certain fractions of the given allergen elicit positive reactions. Thus, Frugoni and Ancona have reported that in some cases of asthma due to grains positive skin reactions were observed only in tests with gliadin or glutenin, and not in response to wheat extract. Hopkins and Kes ten found that some cases failed to react to whole egg, but responded with positive skin reactions to tests with various components of egg injected separately (ovomucin, egg albumin, and globulin).

(7) Absence or diminution of the sensitivity of the skin, owing to

a) Exhaustion of the antibody supply after an allergic attack

b) The fact that in infants the skin may possibly be incapable of producing antibodies,

c) Allergization of an isolated organ (e.g. failure of the skin to react in a gastro intestinal allergy)

d) Fever, hyperemia caused by ultra violet irradiation, sunlight, or rubefacients, marked artificial or natural pigmentation, atrophy or poor circulation of the skin, dehydration in states of poor tissue turgor, mild edema or pre edema,

e) Effects of injection of epinephrine, but only within the first hour (Tuft and Brodsky, Swineford), or of other adrenergic drugs,

f) Inanition, cachexia, or old age,

g) Effects of long sojourn at the seashore (Curschmann)

h) Concurrent infectious diseases (measles, scarlet fever, syphilis) or secondary infection, resulting in metallergic anergy (see p. 30)

(8) Strict localization of the cutaneous hypersensitiveness, so that testing in other skin sites yields negative results

(9) An early stage of development of the hypersensitiveness

(10) Existence of a so called negative phase at the time of testing. These fluctuations are probably the result of a temporary exhaustion of the available tissue antibodies (see discussion of *skeptophylaxis*, p. 212)

(11) Deallergization already achieved. Finally, mention should be made of the so-

called paradox reaction. This term applies to the occasional observation that a greater reaction is caused by a higher dilution of allergen. This can be observed particularly in the responses to tuberculin and trichophyton tests. No satisfactory explanation of this strange phenomenon has as yet been advanced.

3. INDIRECT METHOD OF TESTING (PASSIVE TRANSFER TEST)

The indirect method of testing, by the Prausnitz-Kuestner technic, was first introduced into the routine of diagnosis by M. Walzer in 1927. This method is indicated under the following circumstances:

(1) When the patient's skin presents an abnormal condition, as (a) acute and chronic dermatitis in children or adults, with or without secondary infection, (b) ichthyosis, (c) urticaria; (d) marked dermatographism, (e) a contagious skin infection (e.g., impetigo); (f) universal eruptions; (g) hyperirritability.

(2) In cases of extreme hypersensitiveness in which constitutional reactions resulting from direct testing are feared.

(3) When infants or children are too small or too ill to be subjected to an extensive series of skin tests.

(4) When either the patient or his family strongly objects to direct testing.

(5) When the physician wants to check on the accuracy of an unusual number of positive skin reactions in the course of direct testing.

The clinical usefulness and limitations of the passive transfer method of skin testing have recently been evaluated by Wittich.⁷⁰⁴

TECHNIC. A quantity of 5 or 10 cc of blood is obtained from the hypersensitive patient, provided he is serologically negative with respect to syphilis and free from malaria. This is defibrinated in a sterile centrifuge tube with a sterile glass rod. After centrifugation, the serum is taken up with a tuberculin syringe provided with a $\frac{3}{8}$ -inch, 27-gauge needle, and 0.05 to 0.10 cc. is injected intracutaneously in rows of five or six sites in both upper arms of a recipient. Other skin areas are less suitable, according to Alexander and also to Walzer. The sites should be at least 1 inch apart laterally and 2 inches apart longitudinally. The injected sites should be marked with ink or in some other way, and the allergen extracts injected intracutaneously in the same sites after two to five days. Passively sensitized sites remain sensitive for several weeks, although the sensitization seems to be somewhat less

after four weeks than it is at first. If the tests are made before the subsidence of the reaction to the serum injection, the results are sometimes not quite so reliable as they are a little later. In testing the injected sites, it is important to inject the same extract in an unprepared skin site for comparison. The recipient is first tested to eliminate the possibility that he is sensitive to the allergens used.

Adequate precautions to avoid possible transmission of an infection from one individual to another must be observed. Usually, if a parent, husband, or wife acts as the recipient, it is not necessary to filter the serum, in other cases, it is advisable to filter the serum through a sterile Berkefeld or Seitz filter.

The reaction is to be read after thirty to forty-five minutes. It must be borne in mind that not all recipients accept passive transfer. Elderly and weak individuals are not suitable. Pigmented skin areas are never to be used as test sites. As far as possible, allergic individuals are not to be used as recipients. Recent investigations by Walzer and his collaborators have shown that human antibodies can be passively transferred to the skin of monkeys.

In certain cases of hypersensitiveness with skin manifestations (including infections in which passive transfer with blood serum fails), diagnostic information can sometimes be gained by passively sensitizing a skin site in a normal recipient by the Urbach-Koenigstein method. In this way, it is possible to determine the presence or absence of cellular—rather than humoral—antibodies of the skin. A full discussion of the significance and technic of this method will be found on page 150.

4. PERCUTANEOUS TESTS

In order to obviate some of the difficulties associated with the scratch and intracutaneous technics, especially in the case of children, Moro devised the *inunction* method. This method, however, is suitable only for tuberculin. It consists in gently rubbing a 50 per cent tuberculin suspension into the intact skin over the sternum, previously cleansed with ether, for five minutes. The rubbing can be done either with a finger protected by a rubber cot, or with the rounded end of a smooth test tube. A control site is similarly treated with only the vehicle. A positive reaction is manifested by red papules with a follicular distribution (FIG. 54).

For many years, the application of this method was confined to tuberculin, because

⁷⁰⁴ WITTICH, F. W. *Journal-Lancet* 65: 219, 1945

most other substances could not be carried through the intact skin. Recently however Sulzberger and his associates⁷⁰ have evolved new vehicles that have capacity to penetrate normal skin. With the use of these solvents to which they gave the generic name "penetrasol," the usual protein allergens were enabled to produce a whealing reaction in specifically hypersensitive subjects after thirty seconds of gentle rubbing. The most effective vehicle for transepidermal penetration of powdered

neous tests false negatives were occasionally obtained (Herrmann⁷¹). Although false positives occurred in patients with dermatographism the wheals under these circumstances were atypical. It is to be hoped that this simple painless technic will in time be so thoroughly worked out as to replace the other methods. The injection of allergens is also under investigation as a treatment method by Loveless Sulzberger and others.

Another approach for eliminating the element of trauma in skin testing is the method developed by Abramson⁷² of electrophoretic introduction of the allergens into the skin. He as well as Dutton⁷³ holds that by means of this technic fewer but more specific reactions are achieved than by the scratch method. The test is administered by means of an electrode positively charged with 0.5 milliamperes applied for from two to three minutes. Some ten tests can be undertaken simultaneously. Further investigation will be necessary however before this method can be recommended for general use.

5. PATCH TEST

The functional skin test was introduced by J. Jadassohn in 1894. This important test method was subsequently popularized through the extensive clinical use by B. Bloch in Europe and by Sulzberger in the United States.

The patch test when properly performed and in connection with a carefully taken history is of great value in establishing the etiologic diagnosis of allergic contact dermatitis. It has also been employed for other purposes (see below).

TECHNIC. The test may be applied in various ways depending upon the nature of the substance involved. When a dry powder is to be tested it should be applied to a small area of normal skin and covered with a square of waxed paper or cellophane about 0.5 cm. (1/4 inch) in diameter set in the center of a somewhat larger piece of adhesive plaster of appropriate shape (Fig. 55). Aqueous or alcoholic solutions may be applied to the skin in pieces of 1 cm. or 1.5 cm. (1/2 inch or 3/8 inch in diameter) held in contact with the skin in the same way. Fabrics are employed in the form of one inch squares after first being moistened. Nail polishes lipstick rouge and similar cosmetics may be painted directly



FIG. 54. POSITIVE INJECTION TEST (MORO)
React on to old tuberculin on chest of child
with tuberculosis

allergens was found to consist of an alkyl benzene sodium sulfonate mixture antipyrine water and propylene glycol (Herrmann Sulzberger and Baer^{70b}) and is now commercially available under the name Intraderm. The responses corresponded closely to those elicited by the ordinary scratch test method however, in comparison with the results of intracuta-

⁷⁰ HERRMANN F. SULZBERGER M. B. and BAER R. L. Science 96 451 1942

⁷¹ Idem. New York St. J. Med. 44 2452 1944

⁷² HERRMANN F. Ann. Allergy 3 431 1945

⁷³ ABRAMSON H. A. New York State J. Med. 39 1611 1939

⁷⁴ DUTTON L. O. J. Allergy 11 130 1940

on the skin. In any case, a square of waxed paper or cellophane is necessary to separate the reaction if any, from the non-specific irritation which the adhesive often produces at the edges. Elastopatch⁷² (Duke Laboratories) is very convenient. The patch containing the test substance is usually removed at the end of twenty-four hours. Fabrics, however, may be left in place for two to five days and cosmetics for 48 hours. Plant leaves and oleoresins should be applied for no more than one hour, since they are likely to evoke unduly strong reactions. In every case, however, the patient should be instructed to take away the patch at once if distinct itching or burning is felt and to remove the test substance thoroughly with water, alcohol, or ether, depending on the solubility of the substance.

For patients who are sensitive to adhesive plaster, Grolnick⁷³ has suggested using disks of plain, non-moisture-proof cellophane (moisture-proof cellophane sometimes causes contact reactions¹ of 600 weight, 1

patient and the physician. Moreover, this method may be used to study the influence of controlled alkalinity and acidity on the reactions, by the addition of solutions* of suitable pH through the small opening at the top. The technic is as follows:

A microscope slide is cut with a glass cutter into three equal parts, each 1 inch (2.5 cm.) square and the edges are well smoothed by means of an emery wheel or a suitable file. A strip of adhesive plaster is applied to each of three sides of the glass square, in order to secure it to the skin and at the same time leave a portion of the glass uncovered for the purpose of observation. The substance to be used in the test is placed directly on the skin and covered with the clear portion of the glass square. The ends and free edges of the strips of adhesive tape are then fastened tightly to the skin (Fig. 56).

There are substances that may act as allergens when they come in contact with skin, but are primary irritants

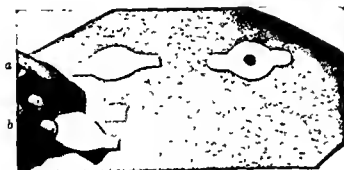


FIG 55

FIG 55 TECHNIC OF PATCH TEST

a = patch test in place b = square of cloth moistened with allergen and ready to be covered c = fenestrated patch test dark-appearing allergen (lipstick) in center

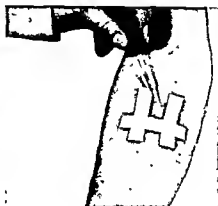


FIG 56

FIG 56 WINDOW PATCH TEST

Particularly useful for study of influence of controlled alkalinity and acidity on reaction

inch (2.5 cm.) in diameter, and special nonirritating collodion (Johnson and Johnson). A test tube without lip is barely dipped into the collodion and a ring is transferred by means of slight rotation to the surface of the skin, thereupon, with the test substance already in place, the cellophane disk is fitted over the ring and held by gentle pressure with a gauze sponge until the collodion has dried. The collodion is easily dissolved by acetone after twenty-four hours. Another advantage of this method is that the reaction can be constantly observed through the transparent cellophane. Downing⁷⁴ advocates the use of Scotch cellulose tape bound with narrow strips of adhesive at the edges to hold the test substance in place.

The so-called window patch test of Guild⁷⁵ also provides constant visibility of the test site for both the

stants when enclosed for the purpose of skin testing, e.g., lacquers, rubber cements, tincture of iodine, etc. For this reason, these materials as well as extracts of plants, essential oils, and substances containing volatile solvents are applied either by wetting the stoppers of the vials containing them and lightly touching these to the skin, or more accurately by the method of Wed-

* For example, Tulipan and Glass⁷⁶ give the following formula for acetic acid perspiration

Sodium chloride	3
Sodium sulfate	1
Urea	2
Lactic acid	2
Oleum	1
Stearin	2
Distilled water	q.s. ad 1000

To make acid, add a drop or two of acetic acid To make alkaline, add a drop or two of ammonia

⁷² TULIPAN, L., and GLASS, F. A. *Indust. Med.* 11: 101, 1942.

⁷³ GROLNICK, M. *ibid.* 7: 341, 1936.

⁷⁴ DOWNING, J. G. - *J. Michigan M. Soc.* 48: 265, 1941.

⁷⁵ GUILD, B. T. *Arch. Dermat. & Syph.* 39: 897, 1939.

roff.³ This procedure consists of dissolving the test chemical or medication in various concentrations in 90 per cent alcohol and applying 1 drop of each concentration to the skin. The alcohol evaporates and the substance remains on the skin. A drop of alcohol is used as a control. No covering should be applied. The reaction appears within a period of from a few hours to twenty-four. Naturally this method can be used only for alcohol-soluble substances. Volatile substances may be tested by having the patient apply his forearm to the open mouth of the bottle containing the solution. Miller has devised a fume test: the volatile substance is poured on some cotton and placed in a small pillbox, the cover of which has several openings. The box is then suspended in another container and fixed to the skin in such a manner that only the

peering after a longer time than this can no longer be considered as a reaction but must be regarded as a true allergization resulting from the testing—an occurrence that is not extremely unusual.

Positive patch tests are with few exceptions characterized by delayed reactions. They are generally graded in the following manner: + for simple redness (FIG 57); ++ for redness, swelling, papule formation (FIG 58); +++ for intense redness, swelling, formation of numerous papules and vesicles (FIG 59); ++++ for large confluent blisters (FIG 60).



FIG 57 Grade 1 sharply defined erythema



FIG 58 Grade 2 numerous papules in addition to erythema and edema

POSITIVE REACTIONS TO PATCH TESTS

vapors of the material contact the skin. These without cover methods have the following advantages: first they simulate more closely the manner in which skin contact is made with plants and other substances in nature; second, the results obtained are uniform while those obtained from the under cover tests although more sensitive are not uniform.

A positive reaction with the ordinary patch test technique usually appears in twenty-four hours though sometimes not until after forty-eight or seventy-two hours. A response ap-

In addition to the positive local reaction focal reactions are occasionally observed in that former test sites flare up or a chronic or healed eczematous patch is exacerbated by the test.

Any skin area may be employed that is not exposed to pressure from clothing and that is not especially involved in the patient's occupational or other activities. It is generally thought that unlike the cutaneous and intracutaneous tests regional differences are not found in the epithelial test except in cases of localized skin allergy. However controlled tests by Ballester and Mom^{6,8} indicate that

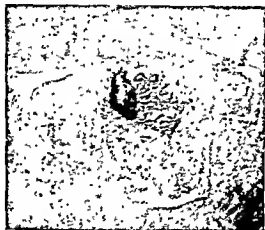
the topographic distribution of patch test reactivity roughly parallels that of the other skin tests, being greatest in a band zone of the arms and forearms in the region innervated by the fifth and sixth cervical and first dorsal spinal roots, with a zone on the back corresponding to the third cervical and second and third dorsal roots being nearly as active. Replies to a questionnaire revealed that the forearm is generally the site of preference of most physicians, although the back, upper arm, thigh, chest, and other areas are chosen by a considerable percentage (Downing¹³).

With new substances, those of varying composition, and those of undetermined allergenicity or toxicity, necessary control tests

primary irritant). For this purpose, the concentration tables in the Appendix should be consulted. Patch testing should never be done during the acute stage of a dermatitis.

CAUSES OF "FALSE NEGATIVE" REACTIONS

The skin area to be tested should not be greasy or oily, since aqueous solutions cannot come into adequate contact with skin covered by a greasy film. Volatile substances must not be permitted to evaporate before being covered by the plaster bandage. Lacquers or varnishes that dry rapidly, and form thin layers, should first be painted on the skin and the test area covered with a small piece of gauze soaked with the same substance. Pow-



POSITIVE REACTIONS TO PATCH TESTS

FIG. 59 Grade 3 vesicles and occasional bullae in addition to papules



FIG. 60 Grade 4 single large confluent bulla.

should be performed, but not on persons with easily irritated skins or with dermatitis, since their non-specific reactions are very likely to confuse the interpretation of the patient's reaction.

It is important to be aware of the possible sources of error inherent in the patch test method.

CAUSES OF "FALSE POSITIVE" REACTIONS

In the first place, one must differentiate between the phenomena of allergic and of toxic reaction. It is necessary, therefore, to know the concentration in which each chemical may safely be used (i.e., in which it does not act as a

dery substances must be applied both dry and in the form of a watery paste.

The patch test often fails because it does not simulate the conditions under which the individual is ordinarily exposed to the allergen in industry or otherwise. Thus, friction, abrasion, maceration, moisture, sweating, cold or heat, and similar influences are factors of great importance in promoting allergization and in causing symptoms. Therefore, the patches must always be applied in such a way that the manner of contact will approximate, as closely as possible, the conditions under which the patient is exposed to the suspected allergen. (An accurate history will enable the physician to visualize and reconstruct, at least in part, the conditions of exposure that apparently led to the dermatitis.) For example, substances

¹³ Downing, J. G. Arch. Dermat. & Syph. 48: 314, 1943

not soluble in water (alkaloid bases or organic acids) should be dissolved in weak acids or alkalies, depending on actual conditions—of course in concentrations that will not irritate the normal skin, as proved by suitable control tests. Similarly, fat soluble substances (e.g. turpentine, benzol, lubricating oils) must be dissolved in fresh olive oil or be mixed with petrolatum. An excellent solvent for fat alcohol, and acetone soluble substances has been introduced by R. L. Mayer—butyric acid amyl ester, a clear colorless liquid, non volatile and nonirritating with an agreeable odor.

Schwartz^{71a} stresses the importance of making epidermal tests with combinations of the suspected substances known to be present in the patient's occupational and other exposures. A thorough knowledge of the technical methods is required on the part of the physician to enable him to choose the correct substances for these tests in different cases. In this respect, Schwartz and Tulipan's^{71b} book is of invaluable assistance.

We have pointed out elsewhere (p. 73) that occasionally the test substance is effective only when the patient is perspiring profusely, since quite often it is only by the action of acid sweat that the allergen is dissolved out, or actually formed. Whether this factor is operative can readily be determined by applying the given substance to the patient's axilla and keeping it there for some time while making him perspire. In testing with protein containing substances such as wool or feathers it is advisable to apply them in a mildly acid medium intended to approximate the normal pH of the skin, which is about 5.3 to 5.8. In this connection Burckhardt's investigations, showing that the allergizing capacity of an allergen is enhanced if it is rather strongly alkaline in nature, may be cited (p. 695).

The original substances should always be used for testing that is, the very ones with which the patient actually was in contact. The reason for this is that the allergizing agent is often not the chemical itself, but certain admixtures or impurities. In occasional cases the patch test will be negative unless performed

during the menstrual period, as shown in 2 cases reported by Tzank and Sidi.⁷² This may possibly be explained by reason of a variation in the level of sensitivity which is higher at this time.

When the patch test proves negative it should be repeated in a previously affected site. On the other hand positive reactions in such sites are to be evaluated most carefully; control tests must be made in the same area in order to determine the presence or degree of non-specific irritability. One of our cases offers an excellent example. A lemon sorter presented a dermatitis of the face. After healing the condition was proved to be due to the volatile oils squirting out from the lemon peel. Tests made by applying pieces of lemon peel produced a vesicular inflammation, but only of the skin of the face. Failure to consider the possibility of local hypersensitiveness is the chief reason for negative reactions in cases of localized dermatitis (Loveman and Simon,⁷³ Hollander^{73a}). The writers were able to show also that in fixed drug exanthems a positive specific skin reaction may be elicited if a patch test is made within the site of the fixed erythema.

A negative patch test does not conclusively prove that the tested substance is not the allergen. Thus the vapor arising from a substance may under certain conditions be the agent responsible. Touraine et al., for instance, have reported on the allergizing properties of trichloronaphthalene, despite negative patch tests among workers in a factory using this chemical. Finally, it must be considered that after a severe outbreak of dermatitis the skin may be refractory to the allergen for some time.

DIAGNOSTIC VALUE OF PATCH TESTS

To begin with, it should be stressed that the patch test—like other types of skin tests—while *specific*, is not necessarily *diagnostic*. In other words, positive results cannot be regarded as absolute proof of the etiologic significance of the substance tested, nor do negative results definitely exonerate it. Each

^{71a} SCHWARTZ L. Am J Pub Health 23: 1049 1933

^{71b} Idem and TULIPAN L. A Text Book of Occupational Diseases of the Skin. Philadelphia Lea 1939

⁷² TZANK A. and SIDI E. Presse med 48: 3 1940

⁷³ LOVEMAN A. B. and SIMON F. A. Arch. Dermat. & Syph. 40: 29 1939

^{73a} HOLLANDER L. J. A. M. A 106: 706 1936

separate test must be evaluated in conjunction with all the other factors, such as the history, the opportunities for exposure, the clinical appearance of the dermatosis, and particularly the results of elimination trials and renewed exposure. O'Leary is correct in insisting that the reaction following a patch test is to be considered not merely in terms of positivity and negativity, but also from the point of view of specificity and nonspecificity.

It has often been suggested that before workers are employed in certain enterprises, they should be subjected to a series of tests with the allergens to which they will be exposed in the course of the work. Extensive investigations have shown, however, that this procedure is of rather limited value, inasmuch as in the overwhelming majority of cases of occupational dermatitis the patients acquire their hypersensitivity in the course of employment. Moreover, pre-employment patch testing seems inadvisable for the reason that workers may be sensitized by the test procedure itself. Industry should test new chemicals on animals and thus discover the sensitizing index of the chemicals rather than of the workers. It is easier to remove the hazard than the workers (Downing).

Recently patch tests have been employed on large groups of persons for the purpose of foretelling whether consumer goods (e.g., wearing apparel, cosmetics, or other articles coming in contact with the skin), industrial materials, or other products are likely to produce dermatitis. This bio-assay for ascertaining the sensitizing capacity of the agent (Sulzberger and Baer,⁷¹ Schwartz and Peck⁷²) is accomplished by two series of patch tests on the same individuals 10 to 28 or more days apart. The first series gives reactions only with primary irritants or with persons previously sensitized. The repetition reveals the number sensitized by the first test. Similar group methods may be used for determining the existing sensitivity of a population to commonly encountered materials and products. Schwartz and Peck⁷² give detailed instructions for testing with fabrics, furs, leather, shoes, rubber, and cosmetics.

6. SCRATCH-PATCH TEST

Tucker and Thomas recommend the use of a combination of the patch and the scratch technic, to be employed in relation not so much to contact dermatitis as to neurodermatitis, where the reaction to the scratch test is often of the delayed type. The material is applied to the skin as in the scratch test, but is then held in place as in a patch test. In this way the development of the delayed reaction is facilitated. The authors call this method the patch-abrasion test, and report success with the technic in cases in which the scratch or the intracutaneous method failed. The present writers have found this technic to be of value, though preferring to call it the scratch-patch test.

The junior author has observed positive scratch-patch tests in one case each of generalized urticaria due to injections of mercupurin and of penicillin, the test also causing a mild flare of the eruption in the former patient. Control subjects failed to react, and scratch, intracutaneous, and patch tests were all negative. Fisher⁷³ successfully used this technic in a series of cases of dermatitis following the local application of sulfonamides.

7 TESTS FOR LIGHT HYPERSENSITIVENESS

Hypersensitivity to light is usually a reaction to the ultraviolet portion of the spectrum, less often to the visible portion, and only exceptionally to the infra-red portion. There is still considerable disagreement as to whether or not there is such a thing as hypersensitivity to X rays (see p. 430). FIGURE 61 presents a summary classifying all known types of rays, expressed in Angstrom units.

To demonstrate the presence of hypersensitivity to light, the patient's skin is directly irradiated with the source of light in question. Comparisons are then made between the patient's reactions to graduated doses (from sub-threshold to normal erythema doses) and those of a normal individual under identical conditions of time, distance, and strength of the lamp or of the light. FIGURE 62 shows the results of such testing with ultraviolet rays of short wave length.

When a case of light dermatosis due to sunlight fails to react to a test with the mercury

⁷¹ SULZBERGER, M. B., and BAER, R. L. 1944 Year Book of Dermatology & Syphilis, Chicago 1st Book Pub. 1945

⁷² SCHWARTZ, L., and PECK, S. M. Pub. Health Rep. 59: 516, 1944

⁷³ FISHER, B. M. J. Australia 2, 194, 1944

arc lamp, it must be concluded that the short-wave ultraviolet rays of the solar spectrum are not the causative factor. In such cases we must therefore attempt to determine which spectral zone is responsible by means of absorbing filters (optical colored glasses) that are known to allow the passage of certain portions of the rays of the spectrum. Application of these filters was suggested by L. Freund and Hausmann, and improved by Urbach⁷²

The light filter we use (FIG 63) is composed of nine colored glasses, about 0.5 mm thick. These glasses are selected to permit the partial

areas are protected by strips of black paper. The areas covered by the filters are then exposed to light of such intensity that a normal control has a mild reaction to that transmitted by the first two filters, which permit passage only of ultraviolet rays of short and long wave length (FIG 65). Under the same conditions a light-hypersensitive patient will react in one or both of the following ways (a) a much more severe inflammatory reaction to the light passing through the first two filters, revealing a hypersensitivity to the ultraviolet rays, or (b) a reaction at one or more of the sites that were covered by the other filters, showing thereby a hypersensitivity to the blue, green, yellow, orange, or red rays of the visible spectrum (FIG 64). By this means the type and degree of his light hypersensitivity can be readily analyzed. It must be mentioned that this

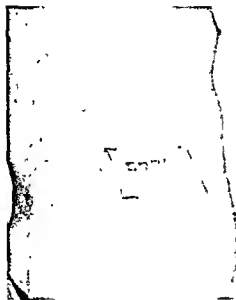


FIG 64 TEST WITH LIGHT FILTER IN CASE OF HYDROA VACCINIFORME

Very marked erythema in sites where ultraviolet light passed through filters, moderate erythema where blue-green and yellow light passed

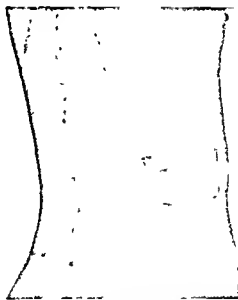


FIG 65 CONTROL IRRADIATED UNDER SAME CONDITIONS

Only slight response at two sites

absorption of the short- and long-wave ultraviolet rays of the visible and invisible spectrum of the sun. The filters are so arranged that the first eight absorb all light except that with wave lengths of 3,750, 4,250, 4,750, 5,000, 5,700, 6,000, 6,300, 6,750 angstroms, respectively—while the last of the glasses transmits the entire ultraviolet and visible parts of the spectrum.

TECHNIC The glasses, fixed in a cardboard holder, are applied to corresponding skin sites of the light-hypersensitive patient and of a normal control, and fastened with adhesive plaster. The surrounding skin

test permits only qualitative evaluation, in practice however, this qualitative light test has proved to be sufficiently accurate

The use of colored filters has one great disadvantage: the patient must sit quietly outdoors for at least two hours even on a clear, sunny summer day. Unfortunately we do not as yet possess any adequate substitute for sunlight. In an attempt to cope with the difficulties arising because of weak sunlight, frequent cloudiness, and cold in the wintertime, the senior author has suggested the use of the so-called light filter chamber. This is prepared by covering the windows of the patient's room

⁷² URBACH E., and KONRAD, J. *Strahlentherapie* 32: 193, 1929

with variously colored gelatin filters the spectra of which have been carefully determined in advance. In this way the patient is exposed for several days each to light of green, yellow, red, and other colors. Thus it is possible to perform the test regardless of the season and of the temperature outside; the cumulative effect of such exposure during several days (if necessary) will make it possible to determine which zone of the spectrum is responsible.

Another source of error lies in the fact that a single irradiation of a normal appearing skin

which the patient is exposed to the light. For example, the test in a case of alcohol pellagra must be accompanied by large doses of alcohol while in other instances the patient must be made to sweat freely and so on.

8 TESTS FOR PHYSICAL HYPERSENSITIVENESS

The skin tests in a broader sense also include methods for determining the reactivity of the cutaneous blood vessels to physical agents.



FIG 66 ECZEMATOUS REACTION TO ULTRAVIOLET RAYS APPEARING AFTER FOUR EXPOSURES OF SAME SITE (a) BUT NOT AFTER TWO EXPOSURES (b)

This demonstrates necessity of repeated exposures to light in suspected cases of solar dermatitis

site of a light hypersensitive patient is often insufficient to call forth an abnormal reaction. FIGURE 66 shows a response to sunlight on the forearm of an individual hypersensitive to light (case of solar dermatitis) with a reaction (b) no stronger than that of a similarly tested normal control; however, after irradiation on four consecutive days the hypersensitive patient showed eczematoid papular inflammation (a) while the control had nothing more than slight pigmentation.

Finally, errors are likely to arise unless due consideration is given to the conditions under



FIG 67 TESTS FOR HYPERSENSITIVENESS TO HEAT AND COLD

Test tubes filled with ice water and hot water respectively and fastened to skin with adhesive tape

It must be noted, however, that positive reactions to these tests by no means prove that the response to cold, heat, or pressure is attributable to an underlying allergy; the reaction may well be based on a pathergic mechanism (p. 411).

The tests for cold and heat are generally performed by applying test tubes filled with ice water or hot water respectively (FIG 67). These are best fastened to the skin by means of adhesive plaster and are left in place for ten

minutes. Another procedure consists in immersing the forearm in cold water (temperature of about 10 C., or 50 F.) or in hot water (40 to 42 C., or 104 to 108 F.) for ten minutes,



FIG 68 POSITIVE URTICARIAL REACTION TO COLD TEST

Test tube filled with ice water applied to skin for ten minutes; control subjects react with only slight erythema.



FIG 69 POSITIVE URTICARIAL REACTION TO COLD TEST

An ice cube was applied to the skin of the forearm for three minutes, and urticarial wheal appeared two minutes after its removal. Configuration corresponds to shape of cube except for downward extension where cold water ran off.

and then allowing the arm to dry in the air. A positive reaction takes the form of urticaria at the site of application of the test (FIG 68) or on the immersed forearm. A simple but effective test for cold urticaria is merely to apply an ordinary ice cube firmly but without

pressure to the test site for three minutes (FIG. 69). A normal response consists of mild to moderate erythema without wheal formation. As E. Freund has pointed out, sometimes the reaction first appears after many hours (delayed reaction).

As explained elsewhere (p. 410) there are some cases that are sensitive only to certain forms of cold (exclusively to cold wind or to



FIG 70 TEST FOR HYPERSENSITIVENESS TO PRESSURE
Weight of 20 pounds suspended from shoulder (or thigh) by broad strap

cold water), and others in which only certain parts of the body react. In such cases, tests must of course be modified to fit these special conditions.

The pressure test is performed by attaching a weight of 10 Kg. (about 22 pounds) to a belt. The belt is then adjusted over the patient's thigh or shoulder, and left for ten minutes (FIG 70). The urticarial reaction may appear within ten minutes, sometimes however considerably later. Urbach and Fasal^{72a} observed

^{72a} URBACH, E., and FASAL, P. *Klin. Wochenschr.* 8: 248, 1929.

positive reactions after from twenty four to seventy two hours (delayed pressure urticaria).

In contrast to the procedure for pressure urticaria tests for urticaria factitia or *dermographism* (FIG 71) are performed by stroking the skin gently. This condition in our experience is hardly ever allergic it is almost always based on a nonallergic pathergy. It should also be noted that according to our experience urticaria factitia and pressure urti-



FIG 71 DERMOGRAPHISM

caria practically never coexist in the same patient.

C INTRAVENOUS TEST

In general the introduction of allergens into the vascular system is strictly forbidden as dangerous to life. Robinson⁷⁶ pointed out an exception however in the test for hypersensitivity to arsphenamine. He found the intravenous test to be the most reliable for determining whether arsphenamine treatment might safely be resumed in the case of patients hypersensitive to this drug. Intradermal tests were found to be useless. Patch tests could be interpreted as contra indications to treatment only if the reactions were strongly positive. A negative patch test does not rule out arsphenamine hypersensitivity.

The intravenous test is to be undertaken after an interval of three months from the date of complete healing or involution of the arsphenamine dermatitis. Intravenous testing is carried out with a sample producing negative or slightly positive patch test reactions but of a different make from that which caused the dermatitis. The initial intravenous dose

is about one tenth the average therapeutic dose that is 0.03 to 0.06 Gm of nearsphenamine or 0.004 to 0.006 Gm of mapharsen. If appreciable itching or erythema ensues the tests and further treatment are stopped. If there are no complaints injections are continued with cautiously increased amounts until the therapeutic dose is reached.

The biologic test for detecting Rh sensitivity (Wiener et al.⁷⁷) is another example of an intravenous test which is useful when there is neither time nor facilities for performing Rh tests and which has the advantage of revealing sensitization to other blood factors as well. Fifty cc of the citrated blood of the prospective donor is administered intravenously and a sample of the patient's plasma taken sixty to ninety minutes later is visually compared with a sample of pretransfusion plasma. If it is not appreciably darker the transfusion can be continued without danger but if it is detectably darker or if there has been a distinct rise in the icterus index hemolysis has occurred and the blood should not be given. In positive reactions the patient not infrequently has a chill and rise in temperature although these findings are inconsistent and may be mild or absent.

D MUCOUS MEMBRANE TESTS

1 CONJUNCTIVAL TEST

The conjunctival test employed at the beginning of the century to demonstrate hay fever (Dunbar) and tuberculosis (Woff Eisner), was soon abandoned because the strong concentrations often brought on severe chemosis. However within the past few years this technique more carefully applied has again found advocates.

In veterinary medicine Calmette's method of dropping a 1 per cent solution of tuberculin on the conjunctiva is now predominantly used.

An interesting and simple procedure was developed by De Besche for testing suspected human hypersensitivity to animal hair or dander. It consists of touching a horse with a finger and then placing the finger gently on the patient's conjunctiva. Persons allergic to

⁷⁷ WIENER A S, SLEZMAN T J and ARONSON W. *Am J Clin Path* 12: 241 1942.

⁷⁸ WIENER A S, WEXLER I B and CAMRIN E. *Am J Dis Child* 68: 317 1944.

⁷⁶ ROBINSON H M. *Pediatrics* 1: 31 J 46: 667 1943.

horse promptly react with a distinctive redness, injection, and sometimes edema of the conjunctiva, as well as a feeling of burning and itching in the eye (FIG. 72).

The conjunctival test—as used, for example, in hypersensitiveness to pollen—should be performed with initial dilutions no stronger than 1:1,000. A drop of this solution is instilled into the lower conjunctival sac. The development, within two to ten minutes, of congestion



FIG. 72. CONJUNCTIVAL TEST (WITH HORSE DANDER)

Reaction expressed by injection and swelling of conjunctiva, with lacrimation

with more or less itching, or of the sensation of having a foreign body in the eye, is interpreted as a positive reaction—i.e., as indicative of specific hypersensitiveness. If no reaction appears within five minutes, the test is repeated with a dilution of 1:100, then of 1:10, and if the result is still negative, the test may be made with the pollen itself.

Sherman and Baron⁷⁹ observed that cases who exhibited focal or constitutional reactions during the course of treatment, not resulting from technical error, accident, or unusual dosage, showed a tendency to a relatively greater reactivity of the conjunctiva as compared to skin (ratio 10:1 or less). However, this was not sufficiently uniform to constitute

a technic for detecting cases subject to untoward reactions.

This test, properly carried out, is harmless, and the reaction can be controlled with 1 or 2 drops of 1:1,000 epinephrine. Since this often has an unpleasant mydriatic effect, Vaughan suggested the following preparation:

	R	Epinephrine hydrochloride 1:1,000	Cc.	
		Saturated boric acid solution	40	5 1
			q s ad 15.0	5 ss

The ophthalmic test is especially useful in detecting the highly dangerous but fortunately rare cases of hypersensitiveness to therapeutic serum. Park recommends instilling 1 drop of it into the lower conjunctival sac. If no reaction (itching, congestion, burning) occurs within ten minutes, the necessary serum may be administered, even if the skin test is positive, for the skin reaction in such a case is not indicative of a dangerous constitutional sensitization. Chobot and his collaborators⁷⁹ recommend eye tests in cases of mold allergy.

2. NASAL TEST

It was Blackley (1873) who first used the nasal test by sniffing up pollen himself to simulate natural exposure. But this procedure often caused such severe reactions that the technic was thoroughly discredited. More recently, however, nasal tests were again undertaken (Duke, Efron and Penfound, Rudolph and Cohen, Blumstein); but although smaller quantities of pollen were used, the tests were still found to be too irritating.

Since 1933, the senior author has been employing the so-called platinum loop method, which has proved to be satisfactory in many thousands of tests.

TECHNIC The end of a platinum loop is flattened in such a way that a surface of about 1 sq. mm. is formed. After it has been flamed and cooled, a tiny amount of talcum powder is taken out of the container and held under one of the patient's nostrils. The smaller end of an ordinary flat toothpick may be similarly employed, of course without flaming. It should not be used more than once. The patient is requested to sniff briefly and energetically, but not so forcibly as to make the pollen reach the posterior nares. Talcum

⁷⁹ SHERMAN, H., and BARON, B. *J. Allergy* 15: 163, 1944

⁷⁹ CHOBOT, R., DUNDY, H. and SCHAFER, N. *J. Allergy* 12: 46, 1940

powder will elicit a reaction very rarely—only when the nasal mucosa is nonspecifically irritable. When there is no reaction the patient is asked to sniff in the same way a tiny quantity of undiluted pollen (Fig. 73). A reaction is considered positive (Fig. 74) when the test produces a typical hay fever attack (tickling in the nose, sneezing, rhinorrhea). When there is no reaction the other nostril should always be tested, since unilateral sensitivity of the nasal mucosa is sometimes encountered. A positive reaction usually begins to disappear spontaneously within five to ten minutes. The next test may then be performed in the other nostril. This can be continued until a strongly positive reaction makes further testing inadvisable at the moment. After an interval of about six hours or more testing may be resumed.



FIG. 73 Insufflation of dry pollen



FIG. 74 Positive reaction to dry pollen

In contrast to the other nasal test methods (in sufflation or spraying of pollen) this technique very rarely brings on too severe reactions—provided of course that the allergen is administered carefully and most sparingly as described above. Furthermore an occasional excessive reaction can readily be relieved by instilling a 3 per cent ephedrine sulfate, 3 per cent propadine or 1 per cent neosynephrin hydrochloride solution. It is in fact always advisable to employ such measures after completing the tests to prevent delayed reactions.

Nasal testing for reaction to pollen may be undertaken at any time of the year except during the hay fever season. If it should seem necessary, however, to subject the patient to this type of test during the hay fever season, it should be performed in an air conditioned room after the patient has been free from all symptoms for twenty-four hours. This method

should also not be employed of course in the presence of any other specific or nonspecific rhinopathy.

Similar nasal tests may be made with flour, house dust, ornith root, feathers, silk, rabbit hair, tobacco, pyrethrum, molds, etc.

The advantage of the nasal test is that it simulates the conditions of natural exposure and that frequently (in 20 per cent of cases according to Efron and Perfound²¹) specific positive reactions are obtained where skin tests have failed. Furthermore a negative nasal test along with a positive skin test strongly

NASAL TEST

indicates that the test substance is not to be considered responsible for the nasal allergy. The objection to the nasal method is that only a few tests can be performed at one sitting. It is advisable therefore to begin testing with those pollens that are not expected to elicit any reaction and to conclude with those more strongly suspected. In this way eight to ten tests can usually be performed at one visit. In our own work we find nasal tests almost always reliable in their application to hay fever patients.

In certain cases the allergen is not the pollen but the volatile oils of blossoms. For example, when tests with linden pollen or jasmine pollen

²¹ EFRON, B. G. and PERFOUND, W. T. *ibid.* 2: 43, 1930.

elicit no response—despite the fact that the patient declares that he always has an attack when standing under a linden tree—the following experiment is to be made. Blossoms (linden, jasmine, or other) are brought into the patient's room at a time when he is free of symptoms. They are carefully covered with organdy of a fine texture. If symptoms appear, they must be due to the volatile substances of the given blossoms, since the pollen cannot penetrate the mesh of the fabric.

3. BUCCAL MUCOSA TEST

Tests may be performed on the buccal mucosa to demonstrate the causative agent of stomatitis venenata, as well as in cases of drug hypersensitiveness in which other test methods fail. Goldman and Goldman⁷³ have described several methods of contact testing the buccal mucosa, of which the most satisfactory employs a rubber suction cup of usual commercial type. The suspected material (liquid, paste, or cream dentifrice or mouth wash, bits of denture or metal) is placed on cotton in the depression and the cup held in place, if necessary, by dental floss wound around the teeth. Reactions have occurred in 5 minutes, with an average of 20 to 30 minutes, although the apparatus may be left overnight. Positive reactions are of four types: (1) simple erythema, (2) erythema and edema—the most common type, (3) ulceration or, rarely, vesiculation, and (4) necrosis.

Following Duke's suggestion of testing drugs on the tip of the tongue, Blank⁷⁴ has advocated having the patient hold a tablet of the drug against the buccal mucosa for ten to twenty minutes. The immediate reaction is edema and occasionally vesiculation, while the 24 hour reaction is vesiculation. The junior author has successfully employed this technic in hypersensitiveness to sulfadiazine, acetylsalicylic acid, and other drugs.

4. BRONCHIAL TEST

The bronchial test was introduced by Peipers,⁷⁵ who had his patients inhale autog-

enous dust extracts. Good results with this method have also been reported by Hofbauer and by Samter.

Since 1935, the senior author has employed an electric inhalation apparatus for bronchial testing. This machine is equipped with a reservoir so constructed that 0.25 cc. of fluid is sprayed within two minutes (Fig. 75). First, physiologic salt solution is used for control purposes, then the allergen is administered in a 1:1,000 dilution for two minutes. If the breathing remains perfectly normal after a

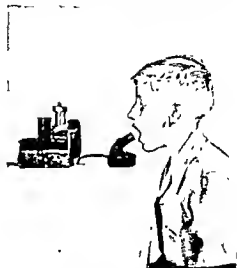


FIG. 75 BRONCHIAL TEST WITH ELECTRIC MICRO-INHALATOR

lapse of one hour, the concentration is increased ten-fold, until a dilution of 1:10 is reached. Only one allergen should be used on any one day, because of the possibility of delayed reactions.

Employing this method, we have been able to demonstrate bronchial hypersensitiveness to pollen, flour, moths, dust, animal hair, and other substances. Responses ranging from difficulty in breathing to a real attack are interpreted as positive reactions, these may be controlled by an epinephrine nebulizer. The extract to be inhaled must contain no phenol or other irritative preservative. We have found glycerosaline extracts suitable. During the hours preceding the test, the patient must not receive any epinephrine either by nebulizer or by injection.

Stevens⁷⁶ compared pulmonary and dermal

⁷³ GOLDMAN, L., and GOLDMAN, B. *Arch. Dermat. & Syph.* 50, 79, 1944.

⁷⁴ BLANK, P. *Md. Surgeon* 92: 419, 1943.

⁷⁵ PEIPERS, A. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 71: 3, 9, 1931.

⁷⁶ STEVENS, F. A. *J. Allergy* 5, 250, 1934.

sensitiveness to inhalants among patients with asthma. In 39 cases in which the skin reactions were strongly positive inhalation of the corresponding extract elicited an attack of asthma in 7 instances, in 33 cases giving moderate and 76 with weak skin reactions the inhalation test was positive in 6 and 2 instances respectively. On the other hand among 410 cases with negative skin tests 10 responded with asthma to the inhalation test.

The bronchial test method seems to be especially valuable in the demonstration of mold asthma since skin tests are frequently of little help here (Flood).

The technic is undoubtedly somewhat troublesome, it is to be employed therefore only in cases in which skin tests have failed, but in which clinical observations suggest the likelihood of an inhalant allergen.

E. PERORAL TESTS

The intracutaneous test is almost totally useless in gastro-intestinal allergy as well as in asthma, migraine, urticaria, and other conditions caused by food allergy. It is now generally recognized that the detection of ingested allergens is best accomplished by tests by the oral route. Three approaches have been elaborated for this purpose: the trial diet, the elimination diet, and the specific propeptan diet. The first method is based on the controlled addition of one food at a time beginning with only sugar and water. The elimination diet employs foods that are relatively non-allergic. While in the diet trial one looks for the reappearance of allergic manifestations the elimination diet is intended to accomplish the opposite—the disappearance of the symptoms. It will be seen that these two approaches are different technics rather than fundamentally different in nature. The specific propeptan method however is based on the principles of skephotaxis (see p. 213).

The physician is occasionally aided in his search for the allergenic food by knowledge of the patient's aversion to certain dishes and to foods prepared in a certain manner. Such indications may prove to be helpful but it is essential that they be confirmed by one of the oral tests. Finally, it must be stressed that the nutritive allergens include not only food proteins but also carbohydrates, fats, salts,

acids, spices and volatile oils. In the majority of instances however a protein is the sensitizing factor.

1. TRIAL DIET

When the history or the clinical course of the allergic disease tends to direct suspicion against a food the so-called trial diet can serve to identify the responsible agent. This method consists in observing the results of the controlled administration of foods.

Brown³⁶ was apparently the first to suggest the systematic addition of trial foods to a basic diet consisting of items to which the patient reacted negatively by skin test. He called this the "food addition method." However, Andresen³⁷ and van Leeuwen³⁸ independently carried this idea to its logical conclusion by commencing with a rice water diet or starvation respectively. Olmsted³⁹ has recently advocated pure amino acids for the same purpose. If unbalanced trial diets are continued for any length of time the administration of synthetic vitamins should be considered.

In order to provide a diet that is for all practical purposes allergen free and at the same time provides for the basal caloric needs of the patients we allow our own cases only sugar and water at the start. This would be contra-indicated solely in the exceedingly rare cases of allergy to carbohydrates.

TECHNIC. The test is best carried out with the patient at home*—preferably in bed—on a daily intake of 300 to 400 Gm. (10 to 13 ounces) of sugar dissolved in water for two days. If the skin or mucous membrane manifestations disappear within this period the patient is given one new food each day, simply prepared and not served in a mixed dish. In order to arrive at an adequate diet as soon as possible it is best to begin with foods that rarely have an allergenic effect, for example the first day's diet may well consist of boiled rice. On successive days one new food may be added as follows: on the second day, potatoes in the jacket.

*BROWN, O. H. *Southwestern Med.* 6: 307, 1920.

³⁷ ANDRESEN, A. F. R. *M. J. & Rec.* 122: 271, 1925.

³⁸ VAN LEEUWEN, W. S. *Van Allergic Diseases*. Philadelphia: Lippincott, 1925.

³⁹ OLMSTED, W. H., HARTFORD, C. G. and HAMPTON, S. F. *Arch. Int. Med.* 3: 341, 1914.

*When children or adults are admitted to a hospital for the diet trial, the diet during the first forty-eight hours should be qualitatively the same as they have been receiving at home. This is to determine whether or not the allergic symptoms were caused by some environmental allergen. If either rhinopathy, urticaria, or other manifestation still persists after forty-eight hours the hospitalization—the nutritional experiment—is begun.

third day, potatoes with olive oil, fourth day, one pound of apples, fifth day, carrots, sixth day, chicken, and so on. If one of these added foods is followed by an attack of asthma, migraine, urticaria, dermatitis, or other symptoms, the suspected item is omitted from the diet. After the allergic symptoms have subsided, this food is again administered, in order to ascertain whether it will again bring on symptoms. If the symptoms do then appear, one nutritive allergen seems definitely to have been found, but the testing must be continued with all the other foods commonly included in the patient's diet, since there are usually several foods responsible in such cases. When neither animal nor vegetable proteins elicit responses, tests must be made with carbohydrates, fats, salts, acids, spices, and volatile oils (consumed, for example, in citrus fruits, flavored candies, chewing gums, etc.)

According to the patient's age and the particular environmental circumstances, the physician's suspicion may be directed toward certain foods: for example, tests must sometimes be performed not only with cow's milk, but also with human and goat milk. Furthermore, as has been mentioned elsewhere (p. 298), the manner in which a given food has been prepared is not infrequently worthy of special attention (raw versus cooked eggs or fruit). The quantity consumed may also play an important rôle: for example, an individual may be able to tolerate a small quantity of milk, but may react allergically to a greater amount. The feeding tests are therefore performed with about the same quantities of a given food as are normally eaten by the patient.* When the physician has good reason to suspect a certain food (e.g., milk, eggs), the test with this substance should be postponed until near the end of the series, by which time the patient will be on a sufficiently nourishing and varied diet consisting of foods proved to be tolerated.

The trial diet is thus a test that can be performed easily enough by almost any ambulatory patient. The physician will be greatly helped if the patient keeps a careful record of all foods eaten, as well as of any general or

local manifestations that may appear. In a similar manner, oral tests may be made with suspected drugs.

The trial diet will, however, be refused by many patients, especially those who are engaged in strenuous work and by the mothers of feeble children, because it produces some undernutrition and sense of hunger.

2. ELIMINATION DIET

Another method of detecting nutritional allergens is represented by the elimination diets. While many authors, including Salomon, Blackfan, Duke, and Alexander, have devised various restricted dietaries, the most useful and effective appears to be those perfected by Rowe.^{710, 711} Except for the milk regimen, these diets have the advantage of containing sufficient amounts of protein, carbohydrates, minerals, vitamins, and calories. As outlined in Table 19, Rowe has suggested four diets: one of them (diet 4) consists of milk, tapioca, and cane sugar, another (diet 3) excludes milk, egg, and cereals; while the remainder consist of foods that have generally proved to cause allergization rarely. Rowe recommends that diet 4 be given first, except of course in cases of hypersensitiveness to milk. If the milk diet is perfectly tolerated, the patient is put on diet 1, in which certain items are omitted or replaced by other substances in the event that positive skin reactions indicate hypersensitiveness. If the patient manifests hypersensitiveness to cereals, he is first given diet 3. *Combinations of these diets* are also feasible, such as diets 1 and 2 combined (particularly in patients intolerant of legumes), or diets 1, 2, and 3 combined. Rowe has recently emphasized the usefulness of a cereal-free elimination diet, consisting essentially of all the vegetables, fruits, and meats in diets 1, 2, and 3, along with soy bean, potato, and tapioca as sources of carbohydrate. Fruit- and cereal-free diets are indicated in some cases. These diets are to be maintained for two weeks or more. When milk is excluded for some time, 4 to 6 Gm. of dicalcium phosphate must be administered daily in order to

* The senior author observed the case of a young man who had urticaria after taking 1½ pints of milk, while ½ ounce of milk evoked no reaction. This seems to contradict the original concept of hypersensitiveness, which involves only the quality and not the quantity of the allergen. Nevertheless, some cases of even a high degree of hypersensitiveness give evidence of being influenced by the quantitative factor. And of course the very principle of hypsensitization is based upon such dilutions of the allergen as will stimulate antibody production without eliciting allergic manifestations. In recognition of this quantitative factor, it is therefore advisable in given cases to undertake *tolerance tests* with increasing amounts of the nutritive allergen.

⁷¹⁰ ROWE, A. H. *Food, Inhalant and Other Clinical Allergy*. Philadelphia: Lea, 1917.

⁷¹¹ *Ibid.* Elimination Diets and the Patient's Allergies. 21 ed., Philadelphia: Lea, 1944.

maintain the mineral balance. Furthermore, the patient must receive Vitamin D. Milk may be replaced by soy bean products or by almond milk.

must be maintained for fourteen days or more, second, in practice it is not readily feasible (if only because of financial considerations) to prepare a diet totally excluding the

TABLE 19—*Elimination Diets (Rouge¹⁴)*

Diet 1	Diet 2	Diet 3	Diet 4
Rice	corn	tapioca	milk*
Tapioca	rye	white potato	tapioca
Rice biscuit	corn pone	bread made of any combination of soy, lima and potato starch and tapioca flours	cane sugar
Rice bread	corn rye muffin		
	rye bread		
	Ry Krisp		
Lettuce	beets	tomato	
Chard	squash	carrot	
Spinach	asparagus	lima beans	
Carrot	artichoke	string beans	
Sweet potato or yam		peas	
Lamb	chicken (no hens)	beef	
	bacon	bacon	
Lemon	pineapple	lemons	
Grapefruit	peach	grapefruit	
Pears	apricot	peach	
	prune	apricot	
Cane sugar	cane or beet sugar	cane sugar	
Sesame oil†	Mazola oil	sesame oil‡	
Olive oil‡	sesame oil	soy bean oil	
Salt	salt	gelatin	
Gelatin	gelatin	salt	
Maple syrup or syrup made with cane sugar flavored with maple	Karo corn syrup	maple syrup or syrup made from cane sugar flavored with maple	
Royal baking powder	white vinegar		
Baking soda	Royal baking powder		
Cream of tartar	baking soda		
Vanilla extract	cream of tartar		
Lemon extract	vanilla extract		

* Milk should be taken up to 2 or 3 quarts a day. Tapioca cooked with milk and sugar may also be taken. Plain cottage cheese and cream may be used.

† May be difficult to obtain. (Pure soy bean oil may be substituted.)

‡ Allergy to it may occur with or without allergy to olive pollen. Mazola oil may be used if corn allergy is not present (or Crisco if allergy to cottonseed is not present).

It is often possible by means of these elimination diets to discover the identity of the allergic food or foods. On the other hand, the elimination diet method has several definite disadvantages. In the first place, each diet

foods most commonly consumed, third—a most important drawback—if one of the first three diets is not tolerated, one cannot know which of the constituent foods are the causative agents. Moreover, they often interpose in

surmountable difficulties for those who must eat in restaurants or boarding houses.

While the principle of the elimination diet has in general been well received, Rowe's speci-

of amino-acid mixtures, dextrose, and cottonseed, corn, or olive oil. Since it is unpleasant to taste, it is sometimes fed by Levine tube. Pure vitamins and salt mixtures were given

TABLE 20—Milk-free Diet

ALLOWED FOODS		
BEVERAGES	DESSERTS	PASTRIES
Cocoa made with water from milk free chocolate or cocoa. Coffee or tea, without milk or cream. Fresh or bottled fruit juices, mineral or carbonated waters.	Fruit gelatins, pudding, shortcakes, or cookies made without dairy products. Fruit ices made with water. Do not use prepared mixes or powders.	Cakes, cookies, and piecrusts made according to recipes recommended by your physician.
BREADS	FATS	SALAD DRESSING
Ry K-rap, corn pone, wheat, rice, rye, graham, and gluten breads, in which no dairy product are used.	Poultry, vegetable, or meat fats, olive oil, or other salad oils. Oleomargarine, if not churned in milk.	French dressing, mayonnaise, or other salad dressings made without dairy products.
CANDIES	FRUITS	SEAFOODS
Made at home without milk, butter, or cream.	All kinds, raw, canned, or plain cooked with sugar, honey, or syrup—served without milk or cream.	All kinds. Use no dairy products in preparation.
CEREALS	MEATS	SOUPS
All kinds, served without milk or cream.	All kinds, prepared without dairy products.	Meat or vegetable soups made at home without dairy products.
EGG DISHES	MISCELLANEOUS	SUGARS
Prepared without milk, butter, or cream.	Potato chips or popcorn prepared without butter. Raisins, nuts, olives, pickles.	Brown, granulated, powdered, confectioner's, maple. Homemade jellies, jams, preserves.
FORBIDDEN FOODS		
BEVERAGES	DAIRY PRODUCTS	MEATS
Chocolate or cocoa unless made with water (Avoid prepared cocoa powder made with dried milk.) Malted milk, or any prepared drink made with milk.	Butter, buttermilk, condensed or dried milk. Cream, curd, ice cream, sherbets. Whole or skimmed milk. Powdered or malted milk. Whey. All cheeses.	Frankfurters or any processed meat to which dried skim milk has been added. Wiener schnitzel.
BREADS	DESSERTS	MISCELLANEOUS
Hot breads such as muffins, popovers, baking powder biscuits, griddle cakes, pancakes, waffles, or doughnuts, unless prepared without milk or other dairy products. Whole wheat bread, white bread, gluten, rye, or graham bread, unless prepared without milk or other dairy products. Zucchini.	Bavarian cream, blanc mange, cakes, and cookies made with milk, cream, or butter. Custards, ice cream, milk or cream sherbets. Pie crusts made with butter. Puddings made with dairy products. Spanish cream.	Fritters. Oleomargarine, if churned in milk. Popcorn, unless prepared at home without butter. Milk chocolate. Prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, piecrust, or waffles.
CANDIES	DISHES PREPARED WITH MILK	SAUCE
All candies, unless homemade without dairy products or ingredients containing dairy products.	Boiled salad dressing, unless homemade without dairy products. Creamed foods, foods fried in butter, scalloped dishes, foods prepared au gratin. Gravies made with milk, cream, butter, or other dairy products. Omelets or scrambled eggs prepared with milk, cream, or butter. Rarebits, soufflés, or timbales.	Milk or cream sauces such as white sauce, butter sauce, or hard sauce.
		SOUPS
		Bisque and chowders, unless homemade with water. All cream or milk soups.
		VEGETABLES
		With butter, milk, cheese, cream, or white sauce.

fications as to the various diets have been considerably modified (Dale and Thornburg,⁷⁴² Waters,⁷⁴³ and others).

Olmsted⁷⁴⁴ has used a diet composed of nutritional factors in nearly chemically pure form for differentiating food allergy from other gastro-intestinal complaints. This consisted

separately. Marked relief was obtained in cases of food allergy.

Since the physician is often asked precisely which foods may be eaten and which must be omitted in a milk-, egg-, or wheat-free diet, as well as in one excluding all three items, we reproduce the tables compiled by the Ralston Purina Company, St. Louis, Mo. (Tables 20 to 23).

⁷⁴² DALE, J., and THORNBURG, H. D. J. A. M. A. 93: 535, 1929.

⁷⁴³ WATERS, L. J. Allergy 2: 223, 1931.

In conclusion, the advantage of the elimination diets over the trial diet consists in the fact that, during the search for the allergen, the patient can be kept on an adequate and relatively varied diet. In order to combine this

3 SPECIFIC PROPEPTAN DIET

The term "propeptan diet" designates the procedure in which the protein contained in each individual food is "neutralized" so to

TABLE 21—*Egg free Diet*

ALLOWED FOODS		
BEVERAGES	FATS	POULTRY AND GAME
Cocoa, coffee, fresh or bottled fruit juices in natural or carbonated waters, tea	Butter —Most poultry or vegetable fats of vegetable oleomargarine	Use no egg products in preparation
BREADS	FRUITS	SALAD DRESSINGS
Rye, crisp corn pone, wheat breads. Rye or rice breads made by an egg free recipe. Most commercial breads have eggs as an ingredient or are brushed with egg white to glaze the top	All kinds raw, canned or plain cooked with sugar, honey or syrup	Made at home without the use of eggs
CEREALS	MEATS	SEAFOODS
Whole wheat cereals, barley, barley flour, corn flakes, corn meal, corn starch, potato flour, rice flakes, rolled oats, rye or tapioca	All kinds prepared without eggs	All kinds. Use no eggs in preparation
DESSERTS	MILK AND DAIRY PRODUCTS	SOUPS
Fruit gelatins, cookies, frostings, cake or pudding made without eggs. Use only recipes recommended by physician	Butter , buttermilk, cheese, cream. Evaporated, condensed or dried milk, whole or skimmed milk	Cream, meat, or vegetable soups prepared at home without eggs or egg products (such as noodles)
	MISCELLANEOUS	SOCAS
	Popcorn, potato chips, raisins, nuts, olives, pickles. Candies made at home without eggs	Brown, granulated, powdered, maple. Home made jellies, jaras, preserves
	PASTRIES	VEGETABLES
	Use only recipes recommended by physician	All kinds, canned, cooked or raw prepared with cream, milk or butter. Do not combine with eggs
FORBIDDEN FOODS		
BEVERAGES	DISHES PREPARED WITH EGGS	MISCELLANEOUS
Coffee, if egg white has been used to clarify it. Root beer which may have had egg added to make it foam. Malted drinks or any prepared drink made with eggs or egg powders	Baked, codified, creamed, deviled, scalloped, fried, poached, scrambled, shirred, hard or soft, cooked eggs, egg drinks, egg sauces, egg whips, or omelets. Do not use dried or frozen eggs in any foods	Griddle cakes, dumplings, pretzels, noodles, marshmallows, soufflé, French toast, fritters, prepared mixes for biscuits, cakes, cookies, doughnuts, muffins or pastries
BAKING POWDER (except Royal)	DESSERTS	PASTRIES
BREADS	Bavarian cream, blanc mange, cakes, cookies, custards, doughnuts, or frostings made with eggs	Macaroons, meringues or pies (such as custard, lemon, coconut and pumpkin). Puddings, unless homemade without eggs. Spanish cream, timbales, waffles
BREADED FOODS	ICE CREAM	SALAD DRESSINGS
If the breading used is an egg mixture	Ice cream, ices and sherbets, unless made at home without eggs from an egg free powder	All salad dressings unless homemade without eggs
BROTH OR CONSUME	MEATS	SAUCES
All broth and consume unless certified as free of egg. Also soups that have been cleared with egg	Sausage, Wiener schnitzel, meat loaf, croquettes or ready prepared meats packed in cans, if that may contain egg white	Hollandaise sauce, Tartar sauce, mayonnaise
CANDIES		SOUPS
Commercial candies brushed with egg white to give them luster—bonbons, almond cakes, fondants, pastes, marshmallows		Mock turtle, consommé, bouillon, noodle or any soup made with egg or from ingredients containing egg

advantage with those of the trial diet, chiefly the saving of time, the senior author,⁷⁴⁹ proceeding from the investigations of Luthlen,⁷⁴⁸ has suggested the *specific propeptan diet* for identifying nutritive allergens.

speaking, by the proper administration of species specific propeptans. Propeptans (see p 217) are protein derivatives obtained from individual animal and vegetable food proteins by digestion with hydrochloric acid, pepsin, and trypsin. While their allergizing effect is attenuated by this chemical action, they still

retain the specificity of the corresponding proteins.

In practice the propeptan diet is carried out by giving the patient only those foods for which propeptans are available

daily. If the intervals between meals are too long for the patient, he may be given lumps of sugar now and then.

TECHNIC One propeptan capsule is taken with water exactly forty-five minutes before a meal. In

TABLE 22—Wheat-free Diet

ALLOWED FOODS		
BEVERAGES	DESSERTS	MISCELLANEOUS
Cocoa, coffee, fresh or bottled fruit juices, mineral or carbonated waters, tea	Bavarian cream, cornstarch pudding, fruit gelatins, homemade wies or ice cream Oatmeal, rice, or rye cookies, tapioca pudding, Indian pudding, Ry-Krisp Crumb Crust	Popcorn, potato chips, cassans and salad dressings if made at home without the addition of wheat products Nuts, olives, pickles
BREADS	FATS	POULTRY AND GAME, SEAFOODS
Ry-Krisp, corn bread, oatmeal or potato muffins made without wheat. Use only recipes recommended by physician	Butter, meat poultry, or vegetable fats Olive oil, oleomargarine	Use no wheat products in preparation
BREADED FOODS	FACTS	SOUPS
In which the breading mixture contains no wheat (Ry-Krisp crumbs may be used for breadings)	All kinds, raw, canned, or plain cooked with sugar, honey, or syrup	Homemade vegetable, cream, or meat soups.
CEREALS	MEATS	STEAMS
Barley, barley flour, corn flakes, corn meal, cornstarch, potato flour, rice flour, rice flakes, rolled oats, rye, tapioca. Ry-Krisp wafers crumbled and served with cream and sugar may be used as breakfast cereal	All meats may be eaten if prepared without wheat or wheat products Ready prepared meats such as corned beef, frankfurters, hamburger, meat loaf, and sausage frequently contain wheat products as fillers	Brown, granulated, powdered, confectioner's, maple Homemade jellies, jams, preserves, candies
BEVERAGES	MILK AND DAIRY PRODUCTS	VEGETABLES
Cereal beverages or coffee substitutes made from wheat. (Information as to ingredients may be found on can or package) Malted drinks, beer, or ale	Butter, buttermilk, cheese, cream, evaporated milk, sces, ice cream, sherbet, whole or skimmed milk	All kinds, raw, canned, or cooked Add only butter, milk, cream, or eggs in preparation. Do not combine with wheat products
BREADS	FORBIDDEN FOODS	MISCELLANEOUS
Hot bread such as muffins, popovers, baking powder biscuits made with wheat products, griddle cakes, waffles, or doughnuts. Wheat breads, crackers (except Ry-Krisp) Gluten bread, graham bread, pretzels, corn bread, or rye bread (unless made at home without wheat flour), white bread, whole wheat bread, bread stuffing, or Zwieback	CEREAL	Gravies, griddle cakes, malt products, waffles, yeast, pretzels, chili con carne, spaghetti, ver macelli, macaroni, or saltines. Prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, or piecrust Yeast cakes
BREADED FOODS	DESSERTS AND PASTRIES	SAUCE
In which the breading mixture contains wheat	Cakes, cookies, custards (unless thickened with eggs or cornstarch), doughnuts, dumplings, puddings, pie, pastries ice cream cones	Butter sauce, cream sauce, or white sauce if wheat is used for thickening
	MEATS	SOUPS
	Ready prepared meats, such as corned beef, frankfurters, or sausage that may contain wheat as a filler Croquettes, fish rolled in cracker meal or crumbs, meat loaf Swiss steak, Wiener schnitzel	Cream, chowder, vegetable, noodle, or meat soups, unless prepared at home without wheat
		VEGETABLES
		Baked beans unless prepared at home without wheat Any vegetables served with a sauce made with wheat flour

It is essential that the propeptan capsules* be administered forty-five minutes before the next meal. Because they are effective only when taken on an empty stomach, meals must be given at intervals of at least four hours. Small children may be fed at intervals of three hours, thus allowing them four or five meals

cases of extreme hypersensitiveness to a certain food-stuff, it may be necessary to ascertain the tolerance to the propeptan by giving one-half or one-fourth of the contents of a capsule. It is absolutely essential that all the protein foods included in the meal should be "neutralized" by the appropriate propeptans. Thus, it is not enough to give merely beef propeptan, for instance, before beef is eaten, regardless of how it is prepared. A meat dish may contain not only meat, but also a number of other ingredients, such as flour, egg, onion, or spices, depending on whether it is stewed, breaded, fried, or prepared otherwise. If propeptans

* Manufactured by Daltre Associates, 2309 Locust Street, Philadelphia 3, Pa.

for these ingredients are available, they must be administered simultaneously with the meat propeptan when the propeptans are not available such ingredients may not be included in the preparation of the

peptans if sensitivity to these foods is suspected. In addition it may be necessary to administer yeast propeptan. When butter is given milk propeptan is indicated when lard pork propeptan. When vege

TABLE 23—Wheat, Egg, and Milk-free Diet

ALLOWED FOODS		
ALL FOODS ON THIS LIST MUST BE PREPARED WITHOUT THE USE OF WHEAT PRODUCTS, EGGS, OR DAIRY PRODUCTS	DESSERTS	PASTRIES
BEVERAGES	FRUIT gelatins, fruit ices or puddings made at home without wheat, eggs or milk. Use only recipes recommended by your physician.	Use only recipes recommended by your physician.
Cocoa made with water. Coffee or tea without cream or milk. Fresh or bottled fruit juices in metal or carbonated waters.	FATS	POULTRY AND GAME
BREADS	Bacon or lard, poultry or vegetable fats. Olive oil or other salad oil.	Do not include wheat, eggs or dairy products in preparation.
Rye, Krip, corn bread, oat meal, rye, potato rye or rye rice bread made without wheat, eggs or milk. Use only recipes recommended by your physician.	FRUITS	SEA FOODS AND FISH
CANDIES	All kinds raw, canned or plain cooked with sugar, honey or syrup—without cream or milk.	All kinds prepared without wheat, eggs or dairy products.
Made at home without dairy products or eggs.	MEATS	SOUPS
CEREALS	All meats if prepared without wheat, eggs or dairy products. Ready prepared meats such as cervelat, frankfurters, hamburger, meat loaf and sausages frequently contain wheat products and skinned milk. Casings may contain egg white.	Homemade meat or vegetable soups.
Barley, barley flour, corn flakes, corn meal, cornstarch, potato flour, rice or rice flakes, rolled oats, rye, tapoca or crumbled Ry-Krip wafers.	MISCELLANEOUS	SUGARS
	Raisins, potato chips (if prepared without butter), nuts, olives, pickles.	Brown, granulated, powdered, confectioner's, maple. Homemade jellies, jams, preserves.
	FORBIDDEN FOODS	VEGETABLES
BEVERAGES	CANDIES	All kinds raw, canned or cooked prepared without wheat, eggs or dairy products.
Cereal beverages or coffee substitutes made from wheat. (Information as to ingredients may be found on can or package.) Chocolate or cocoa unless made with water. (Avoid prepared cocoa powder made with dried milk.) Malted drinks or any prepared drink made with eggs or milk. Beer, root beer or ale.	Unless made at home without eggs or dairy products.	
BAKING POWDER (except Royal)	CEREALS	MISCELLANEOUS
BREADS	Dry or cooked cereals made from or containing whole wheat, farina, or bran.	Milk products: Oleomargarine if churned in milk, gravies, yeast, waffles, fritter, French toast, griddle cakes, pretzels, noodles, Marshmallows, milk chocolate, chili con carne, spaghetti, vermicelli, macaroni or salines. Prepared bread and pastry mixes. Yeast cakes.
Hot breads such as samouffins, pancakes, popovers, baking powder biscuits, griddle cakes, pretzels, waffles or doughnuts. Bread breads such as gluten, graham, white, rye or whole wheat bread. Corn bread, rye bread or bread stuffing unless made at home without wheat flour, eggs or dairy products. Zwieback or crackers (except Ry-Krip). Commercial breads that have egg as an ingredient or have been brushed with egg white to glaze the top.	DESSERTS AND PASTRIES	SAUCES
BREADED FOODS	Bavarian cream, Blanc mange, cakes, cookies, custards, doughnuts, dumplings, frostings, ices or cream, ice cream, cones, Macaroons, meringues, Pies such as coconut, custard, lemon or pumpkin, Piecrust, Spanish cream, Timbales, waffles and marshmallows. Use only recipes recommended by your physician.	Gravies made with wheat or milk products. Butter, cream, hard or white and Hollandaise sauces, mayonnaise and Tartar sauce. Any boiled salad dressing unless made at home.
Unless the breading mixture is free of eggs and wheat.	MEATS	SOUPS
	Croquettes and meat loaf. Ready prepared meats such as cervelat, hamburgers, frankfurters or sausage that may contain wheat as a filler or be packed in casings containing egg white. Wiener, schnitzel, Swiss steak.	Bouques, bouillon, chowders, consommé, cream vegetable, mock turtle, noodle or meat soups unless prepared at home without wheat, eggs, or milk.
		VEGETABLES
		Baked beans unless prepared at home without wheat. Any vegetable served with sauce made with dairy products, eggs or wheat.

dish. In regard to bread it is important to consider whether more than one type of flour was used in its manufacture. Since ordinary rye bread is made from both rye and wheat flour the propeptans for both have to be administered. Moreover, white bread often contains milk, and the crusts of rolls are glazed with egg white necessitating the use of the appropriate pro

peptans must be given and due consideration must of course be given to the various items used in preparing the dish (type of fat, flour, spices). It is not possible to give here all the instances in which protein items occur in masked form in various dishes (for further discussion see p. 298).

It will be seen from Table 24 that as many different propeptan tablets have to be taken before a meal as there are proteins in the foods. Thus, in the example given, four different propeptans are taken before breakfast, nine before lunch, and nine before dinner.

If symptoms are only partially controlled, the desired effect can be achieved by increasing the dose to 2 or 3 capsules for the suspected allergen. In cases in which hypochlorhydria or achylia is suspected, the dissolution of the gelatin capsule may be unduly prolonged;

white bread without wheat propeptan, for example, this bread is again given the following day together with the specific propeptan. If the preprandial administration of the proper propeptan again prevents the appearance of manifestations, the identity of one of the causative food allergens has been ascertained. In this manner, fourteen to twenty days of testing will usually suffice to identify the food-stuffs likely to act as allergens.

Since the complete propeptan diet test, as outlined above, is often too costly, we

TABLE 24.—*Example of a Specific Propeptan Diet for the Identification of Allergenic Foods**

Time	Propeptans	Time	Meal
7:15 A.M.	Orange, wheat, milk, yeast	8 A.M.	Orange juice, wheat cereal, white bread and butter, milk
11:15 A.M.	Beef, wheat, rye, yeast, milk, potato, cocoa, milk, apple	12 M.	Roast beef sandwich on rye bread, mashed potatoes, cocoa, applesauce
3:15 P.M.	Pea, lamb, carrot, rice, wheat, yeast, milk, cocoa, corn	6 P.M.	Split pea soup, broiled lamb chop, carrot, rice, white bread and butter, chocolate cornstarch pudding, milk

* The following propeptans are available

Meats: beef, lamb, pork, veal, chicken

Sea Food: flounder, oyster, shad, shrimp

Dairy Products: milk, American cheese

Eggs: egg, egg yolk

Cereals: barley, corn, oat, rice, rye, wheat

Vegetables: asparagus, bean (baked, lima, soy, string), cabbage, carrot, celery, lettuce, onion, pea, potato (white, sweet), spinach, tomato

Fruits: apple, banana, grapefruit, lemon, orange, peach, pineapple, prune, strawberry

Nuts: peanut

Beverages: coffee, cocoa, tea

Yeast: baker's yeast

hence the patient should be directed to open the capsule and to take the contents with a small amount of water. The same instructions should be given in the rare cases of hypersensitiveness to gelatin. If the objective and subjective manifestations of the disease show improvement within five days—following meticulous adherence to the propeptan diet—the diagnosis of nutritive allergy is established. In order to determine the identity of the food allergen, one propeptan after the other is omitted every second day, while the corresponding foodstuff is retained in the diet. Then when symptoms reappear after ingestion of

have elaborated a so-called *limited propeptan diet*. This method consists of employing only a few types of propeptans, at the expense of variety in the diet (only one meat, two vegetables, etc.). A limited propeptan diet might be composed, for example, of only seven types of propeptans, such as wheat, milk, egg, beef, carrot, potato, and apple propeptan. By the withdrawal of one of the propeptans every second day, while the corresponding food is still ingested, hypersensitiveness to any one or more of the foods in question can be detected. After this procedure has been completed, the presence of

other nutritional allergens may be ascertained by adding a new foodstuff daily without the corresponding propeptan. The sudden appearance of allergic manifestations will direct suspicion to the food item most recently restored to the diet.

If strict adherence to the propeptan diet does not result in improvement of the patient's objective and subjective manifestations, and when nutritive allergy is still suspected, the next step consists of systematic elimination from the diet of carbohydrates, then of fats, and finally of salts as well as of acids. This procedure must surely lead to the discovery of the food allergen, if there is any.

F ENVIRONMENTAL TESTS

It is well known that hospitalization, trips to the mountains, long voyages, and other changes of environment often lead to the disappearance of allergic manifestations. This is true of a large group of diseases, such as many cases of prurigo, lichen urticatus chronic dermatitis, and neurodermatitis, as well as some cases of asthma and vasomotor rhinitis. Thus, in short, absence from the usual environment is often beneficial, while the return home is frequently followed by reappearance of symptoms. This fact alone proves—provided the diet remains the same—that the symptoms are attributable to an exogenous allergen that is to be found somewhere in the patient's environment (house dust, molds, bedding, mattress, pillow, etc.).

The senior author^{74, 75} has suggested using so called day and night tests to identify the agents responsible for such hypersensitivities.

TECHNIC OF DAY TEST After the patient's symptoms have completely disappeared during a stay in the hospital or elsewhere outside his home, he is asked to spend three days at home—but only the daytime. During this time, he is not to be on his bed nor sit on upholstered furniture. When the patient's sojourn in his home under these conditions is followed by recurrence of his allergic symptoms—in a case in which food allergens can be definitely excluded—the possibility of the presence of exogenous allergens within the home must be considered. Common possibilities are rugs, draperies, pets, newly painted furniture and the dust from bedding and upholstery. Other allergens may enter the home through an open window in the form of

animal emanations from nearby stables or of grain dust from an adjacent farm, or of volatile substances (odors) from trees or flowers in the garden. Appropriate tests must be performed to exclude these possible allergizing agents in the given case.

TECHNIC OF NIGHT TEST When the day test is not followed by objective or subjective manifestations, the patient is permitted to sleep at home for three nights. If symptoms recur within this time, the various component parts of the bedding (mattress, pillows, blankets, etc.) must be systematically removed from the room as a test of their allergenic effect.

However, in an appreciable percentage of cases, the patient's allergic symptoms will persist despite removal of all furniture, drapes, and rugs, and even though the patient sleeps on a cot. The most likely explanation in such cases is that the causative agent is to be found in the house dust or molds in the floor or papered walls.

The allergen free chamber, devised by van Leeuwen, constitutes another method of identifying exogenous or home allergens. While a complicated ventilating mechanism was originally necessary to provide filtered air, at present nothing more is required than a small room with an efficient air conditioner. The furniture consists only of a metal bed with wire springs, covered with a new sterilized kapok or rubber foam mattress, and sterilized cotton sheets and blankets. When a patient's asthmatic, nasal, or other symptoms disappear during sojourn in this allergen free chamber, it may be assumed that the allergen is an exogenous agent. Systematically performed exposure and elimination tests may then reveal the identity of the allergens.

Various types of filter masks have been suggested to eliminate certain environmental allergens (Fraenkel and Levy). They are somewhat uncomfortable, however, for which reason they have never been widely employed.

G LEUCOPENIC INDEX

Years ago, Widal reported that the white blood cell count is greatly decreased not only in anaphylactic shock, but also in acute allergic diseases. Joltraan interpreted the hemoclastic crisis test as positive when the decrease in the white corpuscle count exceeded 2,000 per cubic millimeter. Vaughan²¹ employed this principle to identify the food allergen, and on this basis elaborated a diagnostic procedure that he called the leucopenic index (i.e., relationship between fasting and postprandial leucocyte count).

⁷⁴ URBACH, E. Wien klin. Wchnschr. 47: 762, 1932.

⁷⁵ Idem. Muenchen med. Wchnschr. 80: 212, 1933.

TECHNIC Two leucocyte counts, thirty minutes apart, are taken on the patient in a fasting state. After ingestion of the suspected food only, another white blood cell determination is made every 20 minutes for four times and compared with the fasting level. If the number of white blood cells after ingestion is 1,000 lower than before, the result is to be considered positive. At least five to six hours must have elapsed since the previous meal. Another important point is that all the counts should be taken by a single technician, using the same diluting pipettes and counting chamber. Furthermore, it is essential that the patient strictly avoid physical exertion as well as psychic upsets (excitement) both before and during this test. Vaughan states that in 80 per cent of the tests the results correspond with clinical observations. But he concedes on the other hand that repetition of the test quite often yields varying results.

This method has been frequently checked and has met with considerable support as well as criticism. Gay⁷⁴⁷ prefers the postdigestive leucocyte response to all other methods, such as elimination diets, food diaries, skin tests, etc. Rusten,⁷⁴⁵ Rost,⁷⁴⁹ and Schreus⁷⁵⁰ have achieved excellent diagnostic and therapeutic results with this technic, particularly in allergic dermatoses. Rinkel⁷⁵¹ recently pointed out that a decrease in the leucocyte count of much less than 1,000 cells may be significant, and also that the test may be of just as much value in determining which foods are definitely compatible, as reflected in a "trajectory-type" leucocyte curve. He suggested that marked leucopenic responses in the absence of associated symptoms may indicate the occurrence of delayed reactions ten to fourteen hours after the test, or the probability of cumulative reactions. On the other hand, Brown and Wadsworth⁷⁵² studied over 2,000 leucocyte counts, and concluded that there is no physiologic justification of the use of the leucopenic index. Loveless et al.⁷⁵³ disapprove of the method, because in some cases they observed a rise in the leucocyte count despite marked allergic symptoms following ingestion of known allergenic foods. Furthermore, there are disadvantages inherent in this method, in that only one food can be tested on one day and it

is not advisable to perform another test on the following day, since delayed reactions have not infrequently been observed.

The present writers are in full agreement with Vaughan, who, in his book, ends a chapter on the subject with these words: "We must conclude that the leucopenic index is still in the experimental stage and cannot be discussed at this time as a routine diagnostic procedure in allergy."

H ACCELERATED PULSE RATE

Coca⁷⁵⁴ observed that patients allergic to food exhibit an acceleration of the pulse rate, and less strikingly, a fall in blood pressure, when under the influence of an allergen. He therefore devised a system of checking the pulse rate before and after the ingestion of each food. A significant post-ingestive tachycardia indicates sensitivity to the food eaten. The method requires a combination of the trial diet and pulse counts. The patient is placed on a sharply restricted diet for 4 days in order to establish the normal range of the pulse rate. Other foods are then systematically tried, one after the other, and their effect on the pulse rate is carefully recorded. The specific acceleration varies in degree to a maximum of thirty or more beats a minute above the individual's upper normal limit, and usually occurs within one hour. If the results are indeterminate, a second feeding may be tried at once. Recently, Coca⁷⁵⁵ has discussed some of the difficulties in the interpretation of the pulse record encountered in the practical management of cases of food allergy. Rinkel⁷⁵¹ reports some success with this technic, but finds that there are many food allergies not associated with changes in the pulse rate, and also points out that the most valuable feature of the pulse increase is to suggest the occurrence of delayed reactions 10 to 14 hours after the test. If further investigations substantiate Coca's observations, this method could become a valuable diagnostic technic.

I. DANGERS INVOLVED IN ALLERGY TESTS AND THEIR PREVENTION

Every physician who undertakes to perform allergy tests should be aware of the fact that

⁷⁴⁷ Gay, L. P. *J. A. M. A.* 106: 969, 1936.

⁷⁴⁸ Rusten, E. M. *Arch. Dermat. & Syph.* 37: 52, 1928.

⁷⁴⁹ Rost, G. A. *Klin. Wochenschr.* 18: 157, 1939.

⁷⁵⁰ Schreus, H. T. *Muenchen med. Wochenschr.* 86: 1027, 1939.

⁷⁵¹ Rinkel, H. *J. Allergy* 2: 304, 1943.

⁷⁵² Brown, E. A., and Wadsworth, G. P. *J. Allergy* 9: 313, 1938.

⁷⁵³ Loveless, M., Downing, L., and Dorman, R. *J. Allergy* 8: 276, 1937.

⁷⁵⁴ Coca, A. F. *Familial Nonreaginic Food-Allergy*. Springfield, Ill. Thomas, 1943.

⁷⁵⁵ *Idem*. *Ann. Allergy* 2: 2, 1944.

these tests are by no means without danger. It is essential, therefore, that whenever such tests are performed, epinephrine (adrenalin) circulatory stimulants (nikethamide, metrazol), morphine, and oxygen should be instantly available.

Every method is of course capable of producing untoward manifestations. However, those methods in which allergens are introduced into the organism, particularly the intracutaneous tests, are potentially the most dangerous. The sequelae of an intracutaneous test may be of three kinds: (1) very strong local reactions with inflammation even leading to lymphangitis and lymphadenitis, and, in very rare cases, to erysipelas like conditions (Sulzberger), (2) focal reactions in the nose or bronchi, depending on the original shock tissue, (3) systemic manifestations, such as generalized urticaria preceded by severe pruritus and accompanied by headaches, general malaise, nausea, and vomiting. More severe symptoms are rather rarely encountered; these include precordial pain, anxiety, signs of shock (drop in blood pressure), dyspnea, which may even reach a sensation of suffocation, abdominal cramps, severe diarrhea, involuntary urination and defecation and very occasionally tonic convulsions, especially in the extremities.

Other cases, instead of presenting the clinical picture of anaphylaxis, will exhibit a nitritoid crisis. These patients feel a sudden rush of blood to the head with a sensation of great heat and pressure in the head, along with dizziness and ringing in the ears. Objectively there is first a bluish red discoloration of the face, then of the trunk and of the extremities, due to extreme vasodilation. These symptoms are frequently accompanied by a hacking cough or whooping cough like paroxysms, together with nausea.

Systemic reactions have frequently been seen. While it is usually possible to manage them by prompt and adequate therapy (for details see chap XX), occasionally they may lead to death in anaphylactic shock. The following citations represent only a few of the reported deaths directly attributable to *intracutaneous tests*: Baagoe (0.1 cc of egg protein), Cooke (0.02 cc of fish glue), Lamson (0.03 cc of horse serum), Boughton (0.06 cc of horse

serum) Freedman (0.05 cc of horse serum) Vance and Strassmann (silkworm wool ka-pok). Severe constitutional and focal reactions (Randolph,⁷⁵⁶ Swineford^{756a}) and even death (Swineford^{756a}) may occur even though the skin reaction is negative or before there has been time for it to become strongly positive.

While deaths due to *scratch tests* are nearly unheard of and while systemic reactions are far less frequent than with the intracutaneous technique, they are not unknown (see p. 161).

Severe general manifestations have also been observed after *testing by mouth*. As might be expected, gastro-intestinal symptoms are most in evidence here, frequently accompanied by urticaria and angioneurotic edema. There are also several reports of death following ingestion of minimal quantities of various foods: Finkelstein, Finizio, Sales et al. (Wason, Rutinel, and Campbell (milk), Halberstadt (buttermilk), Bowen (egg), von Stark (peas), Benson (cottonseed meal), etc.

The *patch test* method also involves certain sequelae, though of a far less dangerous kind. The local reaction sometimes persists in severe inflammation and pigmentation of long duration, ulceration and severe scarring or keloids are very rarely observed. Furthermore, flares of the sites of skin lesions or previously performed tests are frequently encountered. These flares are sometimes followed by erythrodermas and by general manifestations. Finally, patch tests can produce sensitization, as in 0.08 per cent of the cases observed by Bonnevie⁷⁵⁷ (40 out of 50,000). Epstein⁷⁵⁸ summarizes the hazards of patch testing as sensitization of the tested area, exacerbation of quiescent lesions, generalization of localized eruptions, and possibility of constitutional reactions. The last may occur even though the test is negative (Saunders⁷⁵⁹). The legal aspects of this test method were thoroughly covered by Downing.⁷⁶⁰

The *conjunctival test* can cause severe chemosis and even corneal ulceration. *Nasal*

⁷⁵⁶ RANDOLPH, T. G. J. A. M. A. 126: 430, 1944.

^{756a} SWINEFORD, O. Jr. J. Allergy 1: 24, 1946.

⁷⁵⁷ BONNEVIE, P. Acta dermat. venerol. 20: 632, 1939.

⁷⁵⁸ EPSTEIN, E. J. Invest. Dermat. 5: 50, 1942.

⁷⁵⁹ SAUNDERS, T. S. J. Allergy 14: 76, 1943.

⁷⁶⁰ DOWNING, J. G. Arch. Dermat. & Syph. 44: 63, 1941.

tests can initiate unpleasant and persistent local inflammation, as well as irritation of the paranasal sinuses. Furthermore, these tests may exacerbate an existing asthmatic condition.

Bronchial tests may elicit asthmatic reactions persisting twelve to twenty-four hours despite proper therapy.

The dangers involved in the various methods of testing can be reduced, at least in part, by the following precautionary measures. In the first place it must be emphasized that an accurate and detailed history should be taken before any test is performed. When the patient complains of being particularly sensitive to a certain drug or food, tests with this agent should either not be made at all, or only with special care.

The various methods require different kinds of precautionary measures. These may be outlined as follows:

1. INTRACUTANEOUS TESTS

We have repeatedly pointed out that—with the exception of tests with bacteria or their products, such as tuberculin—it is best first to ascertain the patient's tolerance by means of scratch tests. If they give rise to reactions, intradermal testing might be dangerous. No more than ten tests should be made at one time. If no adverse reaction occurs within ten minutes or so, another ten tests may be performed. Furthermore, in testing intracutaneously, two or more biologically related allergens must never be injected at the same time. For example, tests should not be made simultaneously with several pollen extracts.

Care should be taken about sterility. The patient should not be allowed to leave until about thirty minutes after the last tests are made. Sterile 1:1,000 epinephrine should be kept at hand; at the first danger signal (sneezing, itching of eyes, difficult respiration, or pruritus), about 0.5 cc. should be injected subcutaneously into the region of the reaction, and repeated if necessary. On leaving, the patient should be given one or two capsules of ephedrine sulfate, of 0.025 Gm. ($\frac{3}{8}$ grain)

each, so that he may be able to combat any possible delayed systemic reaction. Such manifestations, often appearing after a delay of several hours, are particularly treacherous, since they may occur despite entirely negative immediate skin reactions (Cooke,¹⁶¹ and personal observations of the writers).

Sulzberger has pointed out that if an injected substance, such as arsphenamine, elicits a positive reaction, and if it is desired to prevent the possibility of sensitization, this can be accomplished by injecting a small quantity of the same substance intravenously twenty-four hours later.

2. PERORAL TESTS

In cases in which the history leads one to expect severe manifestations following ingestion of certain foods, it is advisable to avoid testing with these in raw form. Instead, the well-cooked protein in small doses (about 1 Gm.) may be given. A safer way is to use the specific propeptans derived from the native protein by digestion with hydrochloric acid and pepsin.

3. PATCH TESTS

Needless tests are to be avoided, since, as mentioned above, there is a possibility of producing sensitization. The concentrations used must be nontoxic (correct percentages are given in the tables in the Appendix). In extremely hypersensitive cases, the test substance is to be applied for only a short time (e.g., one hour) and the "without cover" and window patch techniques are to be employed. The patient should always be told that he is to remove the patch at once if he feels any itching or pain. No more than ten tests should ever be applied at once, since there is a possibility of cumulative effect. A preliminary test for hypersensitiveness to adhesive plaster should be made. No tests should be undertaken in the presence of acute skin eruptions. Tests are never to be applied at sites where a strong reaction might be undesirable from the cosmetic point of view.

¹⁶¹ COOKE, R. A. *Ann. Int. Med.* 3: 673, 1930.

CHAPTER XII

PRINCIPLES OF TREATMENT

WE SHALL here consider only the general principles of allergic therapy, while the appropriate treatment of the various diseases of hypersensitiveness will be discussed in detail in the relevant chapters

There are five ways of combating allergic diseases. The method of choice depends on whether the identity of the allergen is known, whether it is feasible to eliminate or to avoid the allergen, whether specific hyposensitization or deallergization is possible, whether the original hypersensitiveness remains monovalent or becomes polyvalent, and on other considerations. The therapeutic approach indicated in a given case must be determined after careful consideration of all these circumstances and sometimes after appropriate therapeutic tests

The five methods of treatment are (1) prophylaxis, (2) specific hyposensitization, (3) heterospecific hyposensitization, (4) deallergization, (5) symptomatic therapy. In addition, attempts must be made to combat the factors predisposing to allergy

A. PROPHYLAXIS

"Since the underlying cause of human hypersensitiveness is unknown, no prophylaxis based on a fundamental etiology is as yet possible"—this pessimistic but justified sentence opens Kern's⁷⁰ article on prophylaxis in allergy. Nevertheless, there are several ways of achieving at least a certain amount of prevention. The prophylactic measures may be divided into three groups

1. PREVENTION OF ALLERGIZATION

As has been shown, it is known that individuals with bilateral inheritance of allergy are especially prone to develop severe allergic conditions. On this ground, it may be advisable for the physician to try to persuade an allergic patient not to marry a mate who also suffers from asthma, migraine, or neuroder-

matitis for fear of passing their hypersensitiveness on to their offspring in enhanced degree

As a general rule injections of foreign serums should be given only when absolutely necessary, since they frequently tend to allergize. Toxoids should be employed in preference, when possible

Expectant mothers who are allergic should take special care during pregnancy to avoid all foods to which they are or were hypersensitive, these precautions may help to prevent allergization of the fetus *in utero*. Moreover, such women should carefully avoid overindulgence in any protein, such as milk or eggs, particularly in the raw state. It must be admitted, however, that as a rule these precautions are of little avail

On the other hand—as Schwartz and his associates⁷¹ have pointed out—the recent alarming increase in epidermal allergization by chemicals, dyes, and wearing apparel can be prevented, at least to a certain extent, by the following measures. When manufacturers use newly developed chemicals in fabrics they should test them on animals for primary irritant qualities by a twenty-four hour patch test, and for sensitizing capacity by a forty-eight hour test made ten or more days after the first one. If this yields a negative result, comparable tests with the fabric itself should be made first on a small and later on a larger number of persons, with appropriate controls. By means of this "prophetic patch test" (Schwartz and Peck⁷²) the "potential sensitizing capacity" (Sulzberger and Baer⁷³) of newly introduced consumer articles intended for use on or next to the skin, or of new substances used in manufacturing processes, may be determined, and makes it possible to screen out those of possible allergenicity and to choose the relatively less sensitizing substance. However, negative results in a test series, even one of considerable size, can never guarantee the absolute innocuousness of any agent

⁷⁰ KERN, R. A. *Ann. Int. Med.* 12: 117-129, 1939

⁷¹ SCHWARTZ, L. et al. *J. A. M. A.* 115: 906, 1940

It is also necessary that the material be so made that perspiration will not dissolve out the dyes, finishes, plasticizers, stabilizers, anti-oxidants, and accelerators used in the manufacture.

2. ELIMINATION OF THE ALLERGIC FACTOR

When the identity of the allergen is known, elimination of it is strongly indicated. The significance of elimination methods is clearly revealed by Rackemann's⁷⁶¹ studies. In a series of 213 asthma cases, 62 (30 per cent) showed definite improvement after the elimination of certain substances. The list of these substances comprises animal substances in 15 cases, feathers in 2, foodstuffs in 7, and dust in 3. In 35 cases the agent was not identified, but the condition improved considerably when the patient changed his residence.

When the allergen can be determined, and when it is of such a nature that it can be more or less readily eliminated, removal of the agent may speedily arrest the symptoms of an asthma or rhinopathy, even of many years' standing. In mild cases of food allergy, it is sometimes possible, particularly when the hypersensitiveness to protein foods has been acquired only recently, to restore tolerance merely by excluding from the diet for a 14 day period all animal protein and the principal vegetable proteins (e.g., legumes, bananas). At the end of this interval patients will often be able to tolerate moderate quantities of the food which previously elicited allergic symptoms. In the great majority of cases, however, the underlying hypersensitiveness disappears—without treatment—only after a long time, if ever.

In dealing with food allergy, it is obviously an easy thing to eliminate such luxury foods as lobster and oysters, or such occasional items as strawberries and chocolate. When the hypersensitiveness is strictly specific, the non-tolerated food can sometimes be replaced with impunity by a similar food (e.g., cow's milk by goat's milk or soy bean milk), similarly, a necessary drug that cannot be tolerated—quinine, for example—can perhaps be satisfactorily replaced by a stereo-isomer (cinchonidine, cinchonine).

The possibility of producing hypoproteinemia by prolonged diets eliminating milk, eggs, meat, or other proteinogenous foods must be kept in mind and, if necessary, prevented by increased allowances of tolerated proteins or by administering amino acids. Hill^{762a} and others have used amino acids in cases of extensive protein allergy, especially in infants, with very favorable results. However, the available preparations also contain proteoses and peptones. It is not surprising, therefore, that in some cases we found these preparations to be allergenic. Careful consideration should also be given to the vitamin content of elimination diets, and the requisite vitamins administered if necessary in synthetic form.

In cases of asthma due to reaction to animals, contact with horses, dogs, and cats is to be avoided as much as possible.

If hypersensitiveness to some part of the patient's bedding is demonstrated, several different approaches can be recommended. One is to replace the allergenic material, such as feathers in pillows or horsehair in mattresses, with substances to which the patient is not sensitive, for example, kapok pillows or rubber foam mattresses are often suitable. However, since it has been observed that patients who are hypersensitive to feathers tend in time to become allergic to kapok and similar substances, we recommend that mattresses and pillows be covered with dustproof casings, equipped with zippers for removal. A simple way to avoid all the common allergens in bedding, at least for a short time, is the use of an ordinary canvas (army) cot without mattresses, pillows, or woolen blankets.

Hypersensitiveness to molds in a damp house can be managed by use of an efficient air conditioner that removes the moisture from the air, and if necessary by pumping away free water from the cellar. This will often afford the patient total freedom from symptoms—at least in the house.

Another form of prophylactic management is climatotherapy in hay fever: during the pollination period of the plants involved, the patient leaves his customary environment and goes to a place that has no such vegetation (mountains, seashore, desert).

⁷⁶¹ RACKEMANN, F. Arch. Int. Med. 41: 346, 1925.

^{762a} HILL, L. W. J. A. M. A. 116: 2135, 1941.

When an apprentice under given work conditions (e.g. baker, carpenter) manifests specific hypersensitiveness (to flour or wood, respectively), the patient is best advised to choose another vocation.

Preventive therapy in allergy includes the avoidance of common colds as far as possible, particularly in the case of asthmatics.

3 ENVIRONMENTAL CONTROL

When house dust has been identified as the cause of an allergic disease, the following instructions are given:

INSTRUCTIONS FOR PREPARATION AND MAINTENANCE OF DUST FREE ROOM

a) PREPARATION

(1) All furniture, rugs, curtains and draperies are to be removed from the room and all closets emptied.

(2) The room including walls, ceilings, closets, spaces behind radiators, and all hidden surfaces, must be thoroughly cleaned, floors and all woodwork scrubbed and the floor waxed.

(3) All wall cracks and holes in the floor or walls around pipes entering the room should be permanently sealed. If hot air heat is used, a dust filter of cotton or glass fiber should be placed behind the grating and changed regularly. When not in use, the register should be sealed off completely.

(4) Screens, ventilators, air conditioners, or air filters are desirable.

(5) Small washable rag rugs and plain washable curtains may be used.

(6) After careful cleaning only the necessary articles of furniture—no upholstered pieces—may be placed in the room. No pictures are to be hung. Bookcases wall hangings, knick knacks are not permitted in the room.

b) MAINTENANCE

(1) The room should be cleaned every day and given a complete cleaning once a week. A damp cloth or *sueden* mop should be used on furniture, the floor, under furniture, on baseboards, moldings, window sills, walls if painted, etc. The room should be aired, and the windows and doors then closed for three or four hours before the patient enters the room.

(2) The patient should be out of the room during cleaning. If a woman is forced to do her own cleaning, a mask of four or more thicknesses of gauze must be worn.

(3) Venetian blinds should be cleaned and rugs washed at least once a week. Curtains are not permitted.

(4) No pets (dogs, cats, canaries, etc.) should be allowed to enter the room. Plants and cut flowers should not be kept in the room.

(5) Only such cosmetics and insecticides (sprays or powders) as are approved by the physician after testing may be used by the patient and others in the household.

Camphor tar and other odoriferous substances are to be avoided.

(6) Doors and windows should be kept closed as much as possible, especially when the room is not in use.

(7) If the patient is a child, only unstuffed washable toys should be allowed and none that accumulate dust.

c) SPECIAL INSTRUCTIONS REGARDING THE BEDROOM

(1) All the directions given above should be followed.

(2) If there is more than one bed in the room, each must be treated in the same way. Metal beds are preferable.

(3) The bed and springs should be scrubbed (outside of the room), the mattress and box spring cleaned with a damp cloth and dried.

(4) Mattresses, pillows and box springs must be completely enclosed in covers made of impervious (allergen proof) materials. Seams should be tightly sewed or a zipper used, and covered with adhesive tape. Alternatively, a foamed latex mattress and pillow may be used. No mattress pad is permitted. Mattresses should be cleaned on both sides with a vacuum cleaner twice a week.

(5) Bedclothes must be fresh laundered. Blankets and spreads, washable. No mattress pad should be used. Fuzzy and unwashed blankets as well as quilts, should be avoided. The bedstead, springs, and all bedclothing must be washed weekly.

(6) Outer clothing such as shoes and coats, as well as household objects should not be kept in the clothes closet.

(7) This room is not to be used for dressing and undressing, it is for sleeping only.

d) GENERAL

(1) Upholstered furniture is best avoided. If it must be used, it can be rendered dustproof by carefully replacing the mush under the decorative fabric and the cambric at the back and bottom, with impervious material. Particular attention must be paid to tacking and sealing the edges and seams.

(2) The floors and furniture in the other rooms must be thoroughly cleaned daily, at a time when the patient is out of the house. Dust should be kept down by the use of a vacuum cleaner and an oiled or damp cloth. The house should then be aired.

(3) Attics, closets, basements, and storerooms are to be avoided.

In cases in which it is desired to test or treat with "autogenous" dust, the patient is given the following directions:

INSTRUCTIONS FOR COLLECTING HOUSE DUST

Since you are suspected of being sensitive to house dust, we must have a sample of the dust from your own home, in order to test you. If you have symptoms while at work, we also need dust from your place of work.

Do not collect the dust yourself, since this might make you worse.

If possible a vacuum cleaner should be used, preferably with a new bag; otherwise, be sure that the bag is thoroughly cleaned before starting. Beat and sweep the mattresses, pillows, upholstered furniture, and drapes, in order to get the dust to the surface before collecting it. Go over the rugs and add the dust swept from the floor. Have the dust from the cleaner bag put into a box. Enough to fill half a shoebox is necessary. Wrap it securely, write your name on the outside, and bring it with you on your next visit.

When the allergic condition is due to factory dust, and when the patient is obliged to continue working at his occupation, he is best advised to make use of a dust respirator.*

Before a child of allergic parents is born, arrangements should be made to prepare the infant's future environment so that there will be a minimum of exposure to inhalants such as feathers, hair, kapok, and dust. In other words, feather pillows, down comforters, woolen blankets, hair mattresses, etc., are not permitted on the infant's bed. Carpets, drapes and curtains are to be removed from the room. The floor should be covered with linoleum. Furry toys should not be allowed, and dogs and cats should be kept away. The mother, nurse, and others should wear simple white cotton clothes, not silk or wool. The child should be kept in his room and not taken elsewhere in the house.

B. DIFFERENCES BETWEEN HYPOSENSITIZATION (DESENSITIZATION) AND DEALLERGIZATION

A discussion of the differences in principle between the methods of hyposensitization and deallergization will be found on page 91. In hyposensitization, supposedly, the antibodies circulating in the blood are markedly increased, while in deallergization the tissue antibodies are neutralized. Thus, the difference between these two most important anti-allergic approaches is a qualitative not a quantitative one (Urbach and Gottlieb^{76a}). Two examples will illustrate this.

Hyposensitization is accomplished, in the case of an individual hypersensitive to pollen, by a

course of subcutaneous injections of pollen in small and systematically increasing dosage, with the result that the blood acquires an *excess of specific antibodies*. When this antigen is encountered later, it is so completely bound by the antibodies circulating in the blood that it cannot enter into contact with the tissue antibodies, which, of course, are the only antibodies leading to elicitation of allergic manifestations. However, when the administration of antigen is interrupted, the antibodies circulating in the blood are gradually eliminated, while the tissue antibodies remain. Hence renewed contact with the antigens will, at a later time, again bring on an antigen-antibody reaction in the tissues, with its allergic consequences.

Deallergization, as used for clinical purposes, is effected chiefly by oral administration of small amounts of the antigen in order to call forth microshocks so mild that clinical symptoms are not produced. For example, an individual hypersensitive to iodide will be given 1 mg. of iodide by mouth and then 0.25 Gm. forty-five minutes later. The first minute quantity of allergen produces within the organism a microshock that is strong enough to neutralize the available supply of antibodies—resulting in a so-called negative or anergic phase. For the duration of this phase, newly introduced antigen encounters no antibodies and thus cannot enter into an antigen-antibody reaction. Antibodies formed subsequently are immediately neutralized by the traces of the antigen remaining within the organism. This results, first, in a temporary state of insensitiveness, and then, following systematic repetition of the procedure, in a permanent state of insensitiveness due to the *absence of antibodies* (for further details, see p. 93).

These two methods have one thing in common—administration of minute quantities of antigen. While deallergization exploits the anti-anaphylactic principle to create the anergic phase, with *arrest of production of specific antibodies* as the ultimate objective, hyposensitization methods employ the device of *quantitatively increased administration of antigen to achieve an increase in antibodies*. (Table 14 outlines the relationship between these two methods.)

* As the Dupo Respirator No. 24 (made by the Portable Lamp and Equipment Company, 72 First Avenue, Pittsburgh, Pa.) or the Wilson Dustite Respirator No. 2 (Wilson Products, Inc., Reading, Pa.), or the no. 5 Bantam Light Weight Respirator (W. S. Wilson, 123 Varick Street, New York City), or the M. S. A. Dustfree or Comfo Respirators (Mine Safety Appliances Co., Pittsburgh 8, Pa.)

^{76a} Urbach, E., and Gottlieb, P. M. *Ann. Allergy* 1: 27, 1943

There is some evidence that methods of hyposensitization under certain conditions particularly if carried out for a number of years, may ultimately lead to deallergization. Thus, after many years of hyposensitization therapy, the number of skin sensitizing antibodies progressively decreases in some patients, to a point at which the serum is no longer capable of transferring sensitivity (Sherman, Stull, and Cooke⁷⁶⁵). It is hoped that future investigation will reveal the conditions under which this stage of decreasing antibody titer can be more quickly and permanently achieved.

C SPECIFIC HYPOSENSITIZATION (DESENSITIZATION)

We understand the term "specific hyposensitization" to designate those methods of treatment by which systematic administration of increasing concentrations of antigen leads to an increase in the number of antibodies. These antibodies, circulating in the blood, can then completely neutralize substantial quantities of antigen, so that the latter cannot react with the fixed antibodies—thus preventing the appearance of allergic manifestations.

Hyposensitization can, in principle, be carried out in different ways. It is preferable to employ, when feasible, the route that will bring the antigen into direct contact with the organ primarily affected—the shock organ. The senior author⁷⁶⁷ demonstrated experimentally that, in cases of hypersensitivity of the skin and of the mucosa to the same agent, epidermal administration of the antigen hyposensitizes only the skin and not the mucosa, while on the other hand epimucous administration affects only the mucosa and not the skin. Failure to meet this requirement certainly explains why subcutaneous treatment so frequently fails in intestinal allergies, why oral administration is ineffective in neurodermatitis, etc. We must differentiate, therefore, between the cutaneous, intracutaneous, subcutaneous, intramuscular, epidermal, oral, rectal, nasal, and bronchial routes of administration—choosing the route according to the particular shock organ.

Methods of hyposensitization consist essentially in administering—by injection, ingestion, application, or spray—a dilution of the antigen just sufficient to elicit a minute reaction in the shock organ and in then repeating the administration when these manifestations of the antigen-antibody reaction have disappeared (about three to seven days). In this way, gradually increasing doses of antigen produce a marked increase in the organism's antibody titer particularly with respect to circulating antibodies.

If, after a while, the administration of antigen is interrupted, there is a gradual decrease of the free antibodies circulating in the blood, while the number of cellular antibodies remains constant, as a result, definite clinical manifestations are elicited when contact is renewed between the antigen and the allergized organs. However, if the patient—as in the perennial treatment of hay fever—receives antigen injections all through the year, and is thus constantly maintaining sufficient circulating antibodies, he can remain free of clinical symptoms. Whether or not this advantageous situation will persist through a second or third hay fever season after therapy is interrupted, we have not as yet had enough experience to say. This method is apparently adequate to bring about clinical insensitiveness to weak allergens or to allergens to which the individual is rarely exposed, but it has been found that this state of relative insensitiveness is likely to be overcome by any massive exposure to the allergen, showing that the tissue antibodies have not entirely disappeared.

Before discussing the various methods of hyposensitization, it might be well to mention one reason for failure inherent in all the methods even if the causative allergen has been accurately identified. One of the main reasons why attempts at hyposensitization often fail is that it is frequently impossible—either because of the patient's circumstances or because of the nature of the allergen—to keep the patient from contact with the allergen during the course of treatment. It may be said categorically that the chances of success of specific hyposensitization in a given case will depend on the extent to which the patient avoids exposure to the allergen during the course of treatment. In some cases it is actually necessary to keep

⁷⁶⁵ SHERMAN, W. B., STILL, A., and COOKE, R. A. *J. Allergy* 11: 225, 1940.

⁷⁶⁷ URBACH, E. *Zentralbl. f. Haut u. Geschlechtskr.* 44: 507, 1933.

the patient in an allergen-free room for a few days (see p. 194).

1. INTRACUTANEOUS, SUBCUTANEOUS, AND CUTANEOUS HYPOSENSITIZATION

Intracutaneous and subcutaneous methods of hypsensitization are the best known and most widely employed procedures intended to increase the antibody content of the blood. Until quite recently, they were, for example, the only known approach in the anti-allergic treatment of hay fever and asthma. There is no sharply defined distinction between these two approaches. Some authors prefer the intracutaneous route, because there is some evidence that the injected substance is absorbed more readily (Feinberg and Bernstein⁷⁶⁵) and because use of this route elicits more rapid and greater production of skin antibodies. However, the majority use the subcutaneous technic. The advantages of the latter are that it is less painful and that it permits the injection of a larger volume of the antigen extract. Both allow of precise dosage, in contrast to the cutaneous method.

Intracutaneous hypsensitization is begun with 0.1 cc. of a concentration ten times more dilute than that which just elicits a positive intracutaneous reaction in the patient. In a majority of cases, this dose is about 0.1 cc. of a 1:100,000 or 1:1,000,000 dilution of the allergen. The course of treatment is then continued in the following manner. If there is no reaction, successive doses are increased by 0.1 cc. of the same dilution of the extract, at intervals of about three days. The amount to be given in one dose by the intracutaneous technic should not exceed 0.3 cc. Then 0.05 cc. of the next concentration, ten times stronger, should be injected, followed by 0.1, 0.2, and 0.3 cc. if the local reaction is no larger than 1 inch in diameter and if no local or general reactions occur. Treatment is continued in this way with the next concentrations, as long as contra-indications do not appear. The maximum dose reached should be continued at weekly intervals for several months, until all clinical manifestations have disappeared. If any injection elicits a severe local reaction or a focal or general reaction, the subsequent injections must be of the same or smaller quan-

ntity, and sometimes even of a weaker dilution of the extract.

The advantages and disadvantages of the *subcutaneous* method are given above. The recommended gradation of doses for subcutaneous hypsensitization will be found in Table 25.

TABLE 25—Schedule of Dosage for Subcutaneous Hypsensitization

Dose No	Amount (Cc.)	Dilution
1	0.1	1:100,000
2	0.2	1:100,000
3	0.4	1:100,000
4	0.7	1:100,000
5	0.1	1:10,000
6	0.2	1:10,000
7	0.4	1:10,000
8	0.7	1:10,000
9	0.1	1:1,000
10	0.2	1:1,000
11	0.4	1:1,000
12	0.6	1:1,000
13	0.8	1:1,000
14	0.1	1:100
15	0.2	1:100
16	0.25	1:100
17	0.3	1:100
18	0.35	1:100
19	0.4	1:100
20	0.45	1:100
21	0.5	1:100
22	0.55	1:100
23	0.6	1:100
24	0.65	1:100
25	0.7	1:100
26	0.75	1:100
27	0.8	1:100
28	0.85	1:100
29	0.9	1:100
30	0.95	1:100
31	1.0	1:100

The dosage given in this table is for patients of about average hypersensitiveness, and may be increased or decreased by the physician according to the patient's reactivity. While a dilution of 1:100 is generally adequate for achieving successful hypsensitization, it is sometimes necessary to resort to a more highly

⁷⁶⁵ FEINBERG, S. M., and BERNSTEIN, T. B. J. Allergy 8, 523, 1957

concentrated extract, such as 1:50 or 1:10. If the patient exhibits a marked local or general reaction following any injection the next dose should be of the same amount or even less. Excessive reactions should be carefully avoided, since they lower the threshold of tolerance and therefore produce unsatisfactory clinical results.

Since children usually tolerate extracts as well as adults, the same dosage schedule may be followed for those over 10 years of age. For younger children and in infants, the dose should be proportionally reduced.

Along with the methods of specific hyposensitization by the intra and subcutaneous routes, we must consider several other methods, which, in the writers' opinion, have been erroneously designated as nonspecific. In cases in which the causal allergen cannot be identified—and especially when it is presumed to be endogenous (see p. 118)—autohemotherapy and autoserotherapy (Achard and Flaudin,⁷⁶⁸ Burgess⁷⁷⁰) as well as autogenous urine (Jausion⁷⁷¹) have long been employed. The beneficial effects of this procedure are now explained by the fact that the systematic administration of the minute quantities of antigen present in the blood or urine of these patients stimulates the production of specific antibodies. This interpretation would also explain why better results are achieved by repeated injections of small quantities of blood or serum (0.1 cc intracutaneously or intravenously, or 1 cc subcutaneously, two to three times a week until ten to twelve injections have been given—Joltrain⁷⁷²), than by less frequent injections of from 10 to 30 cc.

Finally, mention must also be made of the method employing autogenous urinary proteoses, as suggested by Barber and Ortel.⁴⁷⁸ These proteoses, which we have discussed on page 123, probably contain either the primary or the secondary endogenous allergens. The treatment is started with an injection of a 1:1,000,000 dilution, and the course of treatment is otherwise the same as in specific antigen injection therapy.

The scarification or *cutaneous* method should be employed in cases of extreme hypersensitivity, in which intracutaneous administration of the antigen might be dangerous because of too rapid absorption involving possible shock. Especially good results with this method have been reported by Vallery-Radot, Hajos, Reh, and others.

The procedure is as follows. The skin is superficially scratched, the allergen is then rubbed in and allowed to dry. Ortel⁷⁷³ has shown that it is possible to achieve antibody formation by merely spreading typhus vaccine or other antigens over the scarified skin. Since this method is in principle identical with that employed by Jenner for prophylaxis against smallpox, it is aptly called *generalization*.

One more method of specific hyposensitization is still to be mentioned: the conjugation or *haptization* method based on Landsteiner's hapten theory. While it has as yet hardly ever been employed in practice, there are indications that it will be used in the future in the treatment of those allergic diseases that are based on a hapten mechanism. This applies particularly to allergic contact dermatitides in which the causative chemical agent is a partial antigen (hapten), and therefore cannot call forth the formation of antibodies. However, by combining it with a suitable conjugate, such as the patient's blood serum or skin protein, a complete antigen is formed that is capable of inducing specific antibody formation.

2 INTRAMUSCULAR HYPOSENSITIZATION

For many years the intramuscular route for administration of antigen was neglected, but more recently it has been satisfactorily employed. Strickler⁷⁷⁴ and numerous others have administered rhus toxin in this manner. And certain pollen and plant oils that evoke excessive reactions when administered subcutaneously are often well tolerated when administered intramuscularly. Whether or not hyposensitization can be achieved in this manner is still a subject of considerable controversy. It is generally conceded, however, that the principle underlying this method is

⁷⁶⁸ ACHARD C and FLAUDIN C. Bull et mém Soc méd d hôp de Paris 37: 1222-1914, 41: 723-1920.

⁷⁷⁰ BURGESS N. Brit J Dermat 49: 333-1933.

⁷⁷¹ JAUSION H, COR P and SORIER R. Bull et mém Soc méd d hôp de Paris 53: 1378-1417-1929.

⁷⁷² JOLTRAIN E. Rev de méd Paris 48: 267-1931.

⁷⁷³ ORTEL O. Acta dermat 30: 35-1937.

⁷⁷⁴ STRICKLER A. J A M A 77: 910-1921.

sound. Thus Coca has succeeded in hyposensitizing a patient with turpentine allergy (a house painter) by injecting turpentine dissolved in sterile almond oil every seven days.

Furthermore, Bray¹⁹ has developed a "shock method," in which he employs the intramuscular route in order to delay the absorption and thus minimize the hazards. It should be emphasized, however, that this technic is to be used only on hospitalized patients. Bray proceeds in the following way. He prepares the strongest possible solution of the specific allergen, then adds 1:1,000 epinephrine in an amount equivalent to one-fourth of the volume of the solution. A dose of 0.015 cc of this mixture is injected intramuscularly in the buttocks; repeat doses at intervals of three to four days are increased by the same amount (0.015 cc.) each time, until finally a dose of 0.15 cc. is reached, at which point the patient receives only one injection per week. In all, some twelve to fifteen injections are administered. The rate of increase in dosage, as well as the volume of the maximum dose, depends on the tolerance of the patient. In connection with the first few injections—or whenever the patient has untoward symptoms—an additional dose of 0.3 cc. of 1:1,000 epinephrine is administered. The patient must remain under the physician's observation, for general or local manifestations are not unlikely to appear.

3. EPIDERMAL HYPOSENSITIZATION

It was J. Jadassohn^{77a} who discovered that it was possible to achieve first a local and finally a general epidermal hyposensitization by means of repeated epidermal applications in slowly increasing concentrations. Gougerot et al. successfully employed the epidermal route to desensitize patients with dermatitides due to rose wood, paraphenylenediamine, and bichloride of mercury. Stuempke reported similar achievements in dermatitides due to formalin, scarlet red, and tincture of arnica, and Schmidt in relation to mercury and tar dermatitides. Urbach^{84a} was able to cure a weeping dermatitis due to hypersensitiveness to proteins from horses by systematic application of horse serum, sweat,

hairs, and dander, and also succeeded in completely desensitizing a patient with hypersensitiveness to arsenic with this method. Jansson, Lenegre, and Vendel^{77b} claimed to have desensitized cases of contact dermatitis due to hair dye, soap, mustard, rubber gloves, emetine, and vanilla. And Riehl, Jr.,⁶⁹ was able to desensitize a patient with hypersensitiveness to arsphenamine, so that after a while antisiphilic treatment could be resumed with impunity. The allergen application method also achieves hyposensitization in experimental animals (mice allergized to nickel, Milbradt^{77c}, guinea pigs allergized to ragweed, Ginsberg, Stewart, and Becker^{77d}, animals allergized to poison ivy, Keeney^{77e}).

This method seems to have some significance in the prophylaxis of dermatitides due to flowers, grasses, weeds, and woods. The senior author¹⁶⁷ reported successful hyposensitization in a case of hypersensitiveness to sage, Kadisch in a case of dermatitis due to tulips; Blumenthal and Jaffé in a case of allergy to oil of lavender; Maisel, and also Shelmire,^{78a} in dermatitis due to *Rhus toxicodendron*; Touraine and Golé, in dermatitis due to a number of woods. The method of epidermal hyposensitization has been tried not only for sensitiveness of the skin, but also for that of the entire organism. Animal experiments have shown that this is actually possible. Thus, Ishigami, by means of systematic application of egg protein to the skin of rabbits, succeeded in increasing the precipitin titer to the same degree as is attained with intracutaneous injections of the antigen. Hojo demonstrated that immunization could be achieved by inunction of an ointment containing typhoid bacilli that had been killed by heat. (For further references, see p. 690.)

The epidermal method has various advantages over the cutaneous. It is easier to apply, it is painless, considerably less dangerous for allergic individuals because focal reactions when they occur are milder, and a larger surface area is available for reaction.

^{77a} JANSSEN, LENEGRE, and VENDEL. *Bull. Soc. franç. de dermat. et syph.* 35: 164, 1925.

^{77b} MILBRADT, W. *Dermat. Ztschr.* 63: 47, 1932.

^{77c} GINSBERG, J. E., STEWART, C. D., and BECKER, S. W. J. *Invest. Dermat.* 2: 81, 1939.

^{77d} KEENEY, E. L. *J. Allergy* 12: 599, 1941.

^{78a} SHELMIER, B. J. *Invest. Dermat.* 4: 337, 1941.

⁷⁷ JADASSOHN, J. *Klin. Wchnschr.* 2: 1860, 1134, 1923

It simultaneously evokes heterospecific and nonspecific immunizing capacities in the skin, and, finally, it admits of hyposensitization treatment with substances that cannot be administered by injection (physical substances—e.g., light, cold, heat pressure—and certain chemical substances either because they are insoluble, or because of damage to the tissue even when weak concentrations are injected). A Walzer,⁷⁴¹ in some highly interesting experiments, has demonstrated how rapidly percutaneous absorption of antigens takes place. A site on the skin of the arm is passively sensitized with a serum containing antibodies to a specific antigen (e.g., cotton seed). About twenty four to forty eight hours later, the antigen, incorporated in a petroleum base, is rubbed into the skin of the opposite arm. Entrance of the antigen into the circulation is indicated by the appearance of a wheal at the passively sensitized site. The absorption time of cottonseed antigen varies from twelve to twenty minutes.

In certain respects, however, the epidermal technic presents definite disadvantages. It does not permit of the precise, accurate dosage that is possible with the intradermal method, and, above all, weeks and sometimes months of treatment are required before hyposensitization is attained.

It would seem that this method is promising particularly in allergic contact dermatitis, for the immunologic reason that the epidermis is the primary site of the hypersensitivity. Furthermore, the senior author has achieved good results in a case of neurodermatitis (see above). In this condition the shock tissues are the vessels of the cutis. It can be assumed that the specific protein applied to the epidermis is diffused to the allergized structures. This is noteworthy because of the fact that in such highly sensitive cases an attempt to hyposensitize by the cutaneous route, using the scarification method, may have the gravest consequences.

While the discussion above refers to the method of repeated epidermal application of the allergen as a form of *hyposensitization*, the writers feel that it may more properly be classified as *deallergization*. However, since

the necessary immunologic studies have not been carried out to demonstrate whether the titer of the tissue antibodies is increased or decreased as a result of this procedure judgment must be suspended for the time being.

TECHNIC OF EPIDERMAL HYPOSENSITIZATION. Attempts at epidermal hyposensitization should be deferred until the acute cutaneous manifestations have subsided under appropriate dermatologic therapy. Then the suspected allergen must be identified with the patch test method though with use of a concentration ten to one hundred times more dilute than the concentration given in the table in the Appendix. The reason for this is that if too strong a cutaneous reaction is produced there is likely to be a flare of the dermatitis, which is undesirable. Having determined the concentration of the allergen that is just capable of evoking a slight but definite reaction in twenty four or forty eight hours the initial strength for the purpose of hyposensitization should be ten times less. A patch of linen or cotton 1 inch square soaked in this solution is applied to normal skin sites covered with waxed paper or cellophane fixed in place with a gauze bandage and left for twenty four hours. Provided there is no reaction or only a very slight one, the subsequent patches are doubled in size each time until a rather large area of the body is covered. This is done in order to stimulate as much skin as possible to antibody production. Then the concentration is doubled but the size of the patch is restored to 1 square inch. If no undue reaction occurs the same procedure is followed with progressively stronger solutions until a concentration is reached equal to that to which the patient is exposed. As to the frequency of application the best guide is the disappearance of the previous reaction (disregarding pigmentation which often persists quite a while).

Aside from this method, epidermal hyposensitization can also be accomplished by other procedures. Thus Kadisch employedunction with antigen containing salves, e.g., tulip salve in a concentration of 1:100,000. Antigen baths were used by Maisel⁷⁴² to a bath of 45 liters (10 gallons), 1 drop of rhus extract was added by the end of the fourth week, a dose of 450 drops was gradually reached. Kesten and Laszlo⁷⁴³ achieved de-sensitization of a case of dermatitis due to phenyl mercuric iodide by the local application of a dilute solution (1:100,000) for one minute daily, gradually increasing the time to ten minutes. Later the concentration was increased to 1:5,000 for five minutes. Schreus employed the following procedure in bakers

⁷⁴¹ W. WALZER, *F. J. Allergy* 4: 35, 1932.

⁷⁴² M. KESEN, B. and LASZLO, *E. Arch. Dermat. & Syph.* 23: 271, 1931.

with dermatitis of the hands due to hypersensitiveness to ammonium persulfate. The patients knead a dough of kaolin to which a very dilute aqueous solution of ammonium persulfate is added in slowly increasing concentration. Beginning with a 1:100,000 solution, the concentration is increased every day or every other day until a strength of 1:5,000 is attained. The efficacy of this method has been confirmed by Puerckhauer.

Finally, special mention must be made of the electro-osmotic treatment, as introduced by Abramson⁷⁰⁷ and applied clinically by Dutton.⁷⁰⁸ Satisfactory results may be expected of this method, if the assertion is corroborated that substances administered electrophoretically form skin deposits that persist for as long as seven days.

It is possible to achieve hyposensitization by the epimucous route as well as by the epidermal. A case of the senior author's will serve as an example: in a patient with swelling and redness of the mucosa of the gums due to allergy to sage tea, the mucosal reactivity was specifically overcome by gradually increasing the concentration of the sage tea.

In epidermal hyposensitization, by whatever technic, it must be constantly borne in mind that a sudden skin irritation may follow even the slightest increase of concentration, even if the precautionary measures mentioned are most rigidly adhered to. When this happens, treatment should be immediately interrupted for a few weeks and subsequently resumed with cautiously increased dosage. Nevertheless, it will often be found in such cases that the procedure cannot be carried to a concentration necessary for adequate immunologic protection. The same holds true, however, of the intracutaneous and all the other methods of hyposensitization. Nevertheless, since some good results have been reported, epidermal hyposensitization should be attempted in appropriate cases.

4. ORAL HYPOSENSITIZATION

This therapeutic method is based on principles almost as old as the history of medicine itself. According to Pliny, King Mithridates acquired immunity to certain poisons—particularly poisonous toadstools—by taking very

small doses of these poisons to begin with and then larger quantities. Pliny also tells us that snake charmers protected themselves against the otherwise lethal effect of snake bite by drinking water in which the snakes had been living and in which there were traces of snake venom. To this day the French use the term *mithridatism* to designate ingestion first of infinitesimal and then of slowly increasing doses of a poison or other substance. This procedure—as well as the experiments to be discussed immediately below—represents immunization against toxins rather than hyposensitization properly speaking. Nevertheless, the experiments merit brief mention here, since they served as the basis of the methods of oral hyposensitization.

In 1891, Paul Ehrlich achieved the first systematic experimental immunization by mouth when he succeeded in immunizing white mice to ricin by feeding them this poison. Wright, in 1904, using a heat-killed suspension of *Bacillus typhosus*, successfully protected 7 individuals by mouth. In 1908, K. Wolf reported positive immunization experiments in mice by feeding them paratyphoid and dysentery bacilli and other organisms. Calmette achieved effective immunity to tuberculosis in young calves by administering attenuated living tubercle bacilli by the oral route. This method did not become widely accepted and adopted, however, until Besredka had reported his extensive and successful experimental studies. He showed that the administration of bile counteracts the antibacterial action of the gastric juices and also makes the intestines capable of absorbing bacterial antigens, since it frees the intestinal mucosa of mucus and secretions. On the basis of these ingenious experiments enterovaccination against typhoid, paratyphoid, cholera, dysentery, tuberculosis, pneumonia, common cold, scarlet fever, plague, brucellosis, etc., was developed (Vaillant, Kolmer and Rule, Cluver, Hoffstadt, and Tompson; Abe, Boyd, Dick and Dick, and others). While the fact of oral hyposensitization is widely accepted, the explanation advanced by Besredka,¹¹⁸ that oral prophylaxis depends on the development of local immunity of the intestinal wall without the intervention of an antigen-antibody mechanism, has been rejected by most authors.

Grumbach for one reports severe focal reactions in arthritides, as well as the flare up of intracutaneous sites of bacterial tests after administration of vaccines by mouth—manifestations that are the prototypes of antigen antibody reactions. Piper and Dau, Stuart and Krikorian, and Dennis et al demonstrated that introduction of living or killed bacteria into the gastro intestinal tract results in the formation of agglutinins and other antibodies. On the other hand, oral immunization with heat killed bacilli seems to render the intestinal tract refractory to homologous infections before an effective humoral immunity is produced (Torikata and Imaizumi).

Grumbach and Haemmerli reported successful permanent immunization by peroral autovaccine therapy. They began with a dose of 1 cc (containing about 100,000,000 organisms) diluted in an alkaline spring water, this quantity was given every other day for a total of about ten times. Then the dose was successively increased to 2, 3, 5, 10, and finally 20 cc.

Schofield in 1908, was the first to report treatment of severe allergy to egg by oral administration of minute quantities of egg in pills. These findings were confirmed by Schloss and others. But this method received wider recognition only after the systematic experimental work of Kesten, Waters, and Hopkins.⁷⁸⁴ They began with 0.08 mg of egg protein, 0.8 mg of milk protein, and 1 mg of the other food proteins, and increased the dose every fourth day. The dose was decreased if signs of intolerance became evident. It is advisable to have the patient swallow even these small doses of proteins in capsules, since direct contact of the allergen with the mucous membranes of the mouth and throat may bring on severe local swelling. The course of treatment lasts many months. Vaughan, Coke, and Funk, as well as the present writers, have found that good results can unquestionably be obtained by this method, however, as mentioned, the procedure is tedious.

Criep⁷⁸⁵ reported the interesting observation that patients who are allergic to intramuscular

administration of liver extract can be rendered insensitive by taking liver by mouth for a period of time. Furthermore, there are a few reports to the effect that individuals hypersensitive to drugs can be hyposensitized by the oral route. Thus Widal and Vallery-Radot succeeded in curing an allergy to atipynne by administering minute and very gradually increasing doses of the drug. The senior author successfully treated a case of hypersensitivity to quinine in a similar manner. Tate and Klorfajn⁷⁸⁶ reported success in the oral hyposensitization of 30 cases of sulfonamide dermatitis.

Treatment by mouth gained further recognition when good results were reported by the peroral administration of pollens, as well as of grass seed protein, in hay fever. (For further details, see section on hay fever.) For some years attempts have been made to effect peroral hyposensitization in poison ivy, weed, and grass dermatitides. On the basis of the observation that farmers and gardeners hypersensitive to rhus are protected when they chew rhus leaves in the spring, Duncan first systematically employed this method and achieved good results. Schamberg, and later Strickler, then recommended administration of a fluid extract of *Rhus toxicodendron* in increasing drop dosage. Spain and Cooke suggested a modification of this treatment—enteric coated rhus tablets—to minimize the danger of irritation of the oral and gastric mucous membranes. The writers have obtained satisfactory results with enteric coated rhus seed extract. Dieffenbach describes successful hyposensitization by drinking of milk from cows fed with grass and rhus.

Especially extensive and valuable work in this field has been done by Shelmire.⁷⁸⁷ He employs ivy oleoresin (1 per cent in a vegetable cooking oil) placed in an ordinary gelatin capsule. The patient begins with 1 drop of this dilution as the initial dose, and increases the dose by 1 drop every two or three days until a maximum dose of 10 drops daily is reached. This daily dosage is continued until the content of a 1 ounce bottle is exhausted. Unless the patient is found to be abnormally sensitive, the concentration is then increased

⁷⁸⁴ KESTEN B. M., WATERS I. and HOPKINS J. G. *J. Allergy* 6: 431 1935.

⁷⁸⁵ CRIEP L. H. *J. A. M. A.* 119: 506 1938.

⁷⁸⁶ TATE B. C. and KLORFJAIN J. *Lancet* 2: 553 1944.

⁷⁸⁷ SHELMIER B. *South M. J.* 33: 337 1940.

to 2 per cent. The initial dose of this concentration is 5 drops, gradually to be increased to a maximum of 10 drops. Should intolerance to the oleoresins develop, as evidenced by a flare-up of healed patch test sites or a toxic vascular type of rash, treatment should be interrupted and then resumed with a lower concentration. Shelmire's findings were corroborated by Goldman,⁷⁵⁵ who observed a definite diminution or complete disappearance of the patch test reactions in successfully treated cases.

Stratton⁷⁵⁶ succeeded in hyposensitizing guinea pigs by oral administration of whole extracts of poison ivy, as shown by reversal of the previously positive skin test for at least six months.

Shelmire also treated dermatitides in which the cause was established as hypersensitiveness to the pollens of ragweed, cocklebur, and marsh elder, as well as to gaillardia leaves, by oral administration of the specific oleoresins Trunnell⁷⁵⁷ and Sheldon and Blumenthal⁷⁵⁸ reported good results with this method. Finally, house dust allergy can be controlled by the peroral route (Barksdale,⁷⁵⁹ Blackmar,⁷⁶⁰ Urbach). The method is described on page 238.

In connection with oral hyposensitization, the rectal method may be briefly mentioned. Besredka has shown in the experimental animal that this route can be successfully employed. In practice, however, it seldom comes into consideration. In this regard it is interesting to note that V. C. Vaughan was able to relieve a patient with gastro-intestinal allergy due to chicken by means of daily rectal instillations of chicken broth following cleansing enemas.

5. NASAL HYPOSENSITIZATION

In accordance with the principle that the allergen should be brought into direct contact with the shock organ in order to bring about the greatest possible formation of antibodies, efforts have been directed in recent years toward local mucosal hyposensitization. Petragani⁷⁶¹ accomplished this in experimentally allergic animals by nasal instilla-

tion of minute amounts of serum at fourteen-day intervals. Mackenzie⁷⁶² had previously attempted desensitization in hay fever by use of nasal spray of a dilute solution of pollen, and, indeed, was able to lower the degree of the hypersensitiveness to a certain extent. In a case of "baker's coryza" Urbach and Wiethe,⁷⁶⁴ by means of systematic insufflation of flour into one nostril, succeeded in hyposensitizing this one side for several weeks (local hyposensitization). Since the results obtained by the epimucous method were ephemeral, these authors recommended intramucous hyposensitization of the nasal mucosa. The procedure is as follows: if the patient gives a positive cutaneous reaction, treatment is begun with an injection into the mucosa of the nasal septum of 0.02 cc. of a concentration that has been found to evoke no reaction on intradermal testing; 2 drops of epinephrine are added to each cubic centimeter of the solution to prevent the allergen from entering the blood stream too rapidly. With this method we succeeded in desensitizing a number of specific nasal allergies. Hallermann,⁷⁶³ who tested our method, also reported satisfactory results. It must be borne in mind, however, that this type of treatment is by no means free of danger and is therefore to be employed only in a well-equipped allergic institution.

On the basis of the favorable results obtained by Achard and Flandin with daily intracutaneous injections of blood serum, Jacquelin⁷⁶⁵ attempted intramucous hyposensitization with autogenous serum, especially in cases of rhinopathy and asthma in which the allergen could not be identified.

TECHNIC. Under aseptic precautions, 10 cc. of blood is withdrawn from the patient's vein (the fresher the serum, the better the effect; serum taken at the very beginning of an attack is particularly effective). After coagulation, the blood clot is removed with a platinum loop and the serum is injected by means of a special syringe into the mucous membrane above the lower turbinate or into the mucosa of the nasal septum. The injection into the mucous membrane must be made in

⁷⁵⁵ GOLDMAN, L.: *Am. J. Dis. Child* 64: 241, 1942.

⁷⁵⁶ STRATTON, E. K.: *California & West. Med.* 54: 115, 1941.

⁷⁵⁷ TRUNNELL, T. L.: *J. Iowa M. Soc.* 30: 390, 1940.

⁷⁵⁸ SHELDON, J. M., and BLUMENTHAL, F.: *Am. J. M. Sc.* 262: 93, 1941.

⁷⁵⁹ BARKSDALE, I. S.: *M. Rec.* 144: 76, 1936.

⁷⁶⁰ BLACKMAR, G. M.: *J. A. M. A.* 78: 787, 1922.

⁷⁶¹ PETRAGANI, O.: *Mécl. Welt* 7: 738, 1933.

⁷⁶² MACKENZIE, G. M.: *J. A. M. A.* 78: 787, 1922.

⁷⁶³ HALLERMANN, O.: *Mécl. Welt* 7: 738, 1933.

⁷⁶⁴ URBACH, E., and WIETHE, C.: *Muenchen med. Wchnschr.* 78: 1470, 1931.

⁷⁶⁵ JACQUELIN, A., TCHIR, J., DAVOCS, and REVEILLAUD, B.: *Et. méd. Soc. méd. hôp. de Paris* 45: 557, 1912; JACQUELIN, A., and BONNET, G.: *Presse méd.* 42: 249, 1934.

such a way that an edematous intramucous elevation results. To avoid the fairly severe pain caused by the injection, local anesthesia may be produced by applying a 4 per cent solution of novocain. In all twenty injections of blood serum, each of 0.3 to 0.5 cc. are made on consecutive days. In the majority of cases a temporary exacerbation of the condition is observed following the fourth or fifth injection, after the tenth to twelfth injection however marked improvement occurs either gradually or suddenly.

H. Gold, as well as Fraser et al., has recently employed the nasal route for immunization to diphtheria. These authors repeatedly applied a concentrated diphtheria toxoid to the nasal mucous membrane.

6 BRONCHIAL HYPOSENSITIZATION

Alexander, Becke, and Holmes³¹ demonstrated that guinea pigs that had been allergized by way of the bronchi could subsequently be hyposensitized by repeated inhalation of the antigen. These experiments were confirmed by Kallós and Pagel.³² It is also possible to employ bronchial hyposensitization in man, as shown by Hofbauer.³³ He succeeded in hyposensitizing patients who reacted with asthma to a certain dust forming type of stone (flysch), by means of spray inhalation of water into which flysch dust had been shaken. Brown, Irons, and Rosenthal³⁴ observed that repeated inhalation of the fumes from boiling suspensions of dead tubercle bacilli by laboratory workers resulted in a marked decrease in cutaneous sensitivity to tuberculin. In two cases with recurrent tuberculous iritis, freedom from symptoms followed repeated exposure. Animal experiments showed that sensitized guinea pigs could be similarly desensitized. This method of treating asthma has not been frequently employed, it seems promising enough, but presents considerable difficulties in practice. Animal experiments have convinced us that we are not as yet capable of finding a concentration that has a hyposensitizing action and that may not at the same time elicit asthma. As a rule, weak concentrations even when employed over a period of time, have no appreciable effect, while somewhat stronger concentrations evoke an asthmatic response.

Nevertheless, this approach certainly merits attention and further study.

Silberschmidt, and Matsumoto and Saito showed in a series of experiments that the inhalation procedure will immunize animals to diphtheria and tetanus.

7 DANGERS INHERENT IN HYPOSENSITIZATION METHODS

Not infrequently anaphylactic manifestations are elicited by intra- and subcutaneous administration of allergens, and also, although less frequently, by intramuscular or peroral administration. The anaphylactic response may take one of three forms. In the first, a huge local reaction appears at the injection site, with redness and swelling, associated with unbearable itching. These manifestations then spread over the whole arm and subsequently over the entire body. During this stage coryza and asthma appear, even if the latter condition has never previously been present. In the second form, local manifestations at the site of injection are entirely absent, but more or less generalized mucosal and cutaneous reactions appear. They include lacrimation, severe sneezing, rhinorrhea, swelling of the eyelids, edema of the face, and, not infrequently widespread urticaria, along with general malaise. In the third form, there are no cutaneous or mucosal symptoms, at least not in the beginning, but a clinical picture dominated by collapse and severe diarrhea. In some cases the patients complain of severe pain in the abdomen (abdominal crises) and of vertigo. Occasionally dysmenorrhea appears. The uterus may, indeed, undergo violent contractions, resulting in abortion in pregnant women (Hansen,³⁵ Francis³⁶). (For this reason, hyposensitization in pregnancy should be carried out with caution.)

The element of danger inherent in the intra-cutaneous and subcutaneous hyposensitization methods—and to a lesser degree in the oral, nasal, and bronchial procedures—is emphasized by the reports of deaths of patients under treatment even at the hands of highly experienced and careful specialists. (For references, see discussion of dangers inherent in

³¹ HOFBAUER L. Wien klin. Wchnschr. 45: 298 1932.

³² BROWN E. V. L. IRONS E. E. and ROSENTHAL S. R. Arch. Ophth. 28: 1028 1942.

³⁵ HANSEN K. Deutsche med. Wchnschr. 59: 206 1933.

³⁶ FRANCIS N. J. Allergy 12: 553 1941.

allergic tests, p. 195.) Cooke³⁹¹ states that the rate of untoward incidents of all sorts in specific hyposensitization, including tests, is 10.6 per cent.

The dangers of hyposensitization can be considerably decreased by careful adherence to the measures described on page 197 for the prevention of anaphylactic manifestations in allergic tests. Furthermore, it is advisable to accompany administration of the allergen with from 0.2 to 0.4 cc. (3 to 6 minims) of a 1:1,000 solution of epinephrine in all cases in which either the history, or anaphylactic symptoms previously observed by the physician, indicate the possibility of special danger. This can be done by drawing up the desired amount of epinephrine hydrochloride into the syringe containing the extract. A substantial increase in the volume of liquid in which the allergen is dissolved also tends to delay absorption and to diminish constitutional reactions. As a further precaution, a blood pressure cuff may be placed high on the arm without pressure. The injection is made subcutaneously below the cuff. Should a reaction occur, the cuff is inflated to a level between systolic and diastolic pressures, and epinephrine is injected into the other arm. The cuff pressure may be gradually reduced after the reaction has subsided.

D. HETEROSPECIFIC HYPOSENSITIZATION

By heterospecific hyposensitization is meant the use of hetero-antigens in order to call forth the production of *specific* antibodies (for further explanation, see p. 92). It is this fact of the increase of specific antibodies that distinguishes this approach from that of nonspecific hyposensitization. The former refers to the administration of systematically increased small doses of hetero-antigens—as, for example, peptone, tuberculin, stock vaccine, etc.—this bringing about a great increase in the number of specific antibodies in the blood.

It should be pointed out, however, that the concept of heterospecific hyposensitization as the mechanism underlying the use of tuberculin, peptone, and other substances, is not shared by all workers in this field. The

majority speak of “nonspecific” desensitization, by which they mean to designate the reduction of exaggerated reactivity by measures other than immunobiologic. The German immunologists employ the term *Umstimmung* (changed reactive capacity or “retuning” of local cells—F. P. Gay.) According to Weichardt, the effectiveness of “nonspecific therapy” with physical or chemical agents is to be explained by the formation of intermediary split products that stimulate the entire body to increased immunologic activity. If the organism is allergic, this results in the production of specific antibodies—i.e. specific immunization is brought about nonspecifically. This concept is not so far removed from our own.

In this connection the studies of Maunsell³⁹² on the local hyposensitization of the skin of multisensitive patients are worthy of mention. She found that one allergen can hyposensitize the skin so that it will no longer react to the others, and termed this “cross desensitization.” Depending on the relative cutaneous activity of the allergens, the cross desensitization may be either reciprocal or unilateral, but in either case is independent of the biologic group of the allergens, and is the result of an anti-allergic mechanism and not merely of a general refractoriness of the tissues. On this basis, Maunsell holds that a patient with multiple sensitiveness does not require a mixed extract, but treatment with a single allergen carried as far as possible, with the strongest attainable concentration. This conclusion requires confirmation.

Peptone in the treatment of asthma was first employed by Auld. He administered it intramuscularly and even intravenously. The subcutaneous route is now employed exclusively.

TECHNIC The treatment is begun with a preliminary intracutaneous injection of 0.05 cc. of a 5 per cent solution. If there is no response, or if the reaction is only slightly positive (diameter less than 5 mm or $\frac{3}{16}$ inch), it is apparent that no increase in antibody production can be expected. In the great majority of cases, however, the skin reaction is so strong (urticarial wheal about 2.5 cm. or 1 inch in diameter, with pseudopodia) that treatment must be initiated with a 1 per cent—and in some rare cases even with a 0.1 per cent—

³⁹¹ COOKE, R. A. *J. Immunol.* 5: 219, 1922

³⁹² MAUNSELL, K. *Lancet* 1: 5, 1943

solution. These injections should be given subcutaneously in order to avoid allergization of the skin as a result of repeated intracutaneous injections. In accordance with the principles outlined on page 203, the doses are gradually increased from 0.05 to 1.0 cc, and the concentration from 1 to 5 per cent. At first the injections are given three times a week, then twice a week, and finally once a week comprising a total of fifteen or twenty injections. When indicated the course of treatment may be repeated after a rest period of two to three months, beginning again with rather small doses. We must emphatically warn against intravenous administration of peptone.

Peptone therapy is valuable in cases of asthma, rhinopathy, persistent urticaria, and angioneurotic edema in which the causative allergen cannot be identified.

Vallery Radot and Blamoutier observed that somewhere between the eighth and twelfth injections in this course of treatment some patients had severe reactions. These took the form of a large edematous plaque with an erythematous periphery, or, in occasional instances, of a pseudophlegmonous reaction and even of an aseptic abscess. These manifestations are to be considered as the result of cutaneous allergization (Arthus phenomenon). Despite rather extensive use of this method, the senior author has seen such a severe reaction only twice.

Tuberculin treatment, as introduced by van Leeuwen, constitutes another method of heterospecific hyposensitization. But it should be used only in cases that are hypersensitive to tuberculin, without any other evidence of tuberculosis.

TECHNIC In order to obtain satisfactory results the patient must have a strong local reaction to 0.1 cc of a 1:100,000 dilution intracutaneously. The course of tuberculin treatment is then begun with 0.1 cc of a 1:10,000,000 dilution subcutaneously, or of a 1:1,000,000 dilution in the case of relatively less hypersensitive individuals. At first, injections are given twice, then once a week later every second and finally every fourth week, and are continued for many months.

Employing this method, the authors frequently achieved good results in cases of pathergic asthma and rhinopathy.

The same principle (i.e., stimulation of the organism to increased production of specific antibodies) might well explain the good results obtained with injections of *foreign protein* such as milk (aolan) or stock vaccines. More

over, treatment with sulfur,* especially colloidal sulfur, should also be mentioned here. It seems most likely that these methods act by reason of the local breakdown of the body protein resulting from the inflammation produced by the injected substances. These altered proteins constitute hetero antigens that stimulate production of specific antibodies. In addition, all forms of fever therapy (e.g., with typhoid vaccine), the effects of intercurrent infections (e.g., erysipelas), exposure to sunlight, and strong roentgen irradiation, may also be included here.

E SPECIFIC DEALLERGIZATION

The term deallergization designates all therapeutic measures by means of which the antibodies actively produced by the organism are either neutralized by the adequate introduction of antigens or are in some other way rendered incapable of reacting. The result is, first, the consumption of the supply of specific tissue antibodies, and, second, the eventual cessation of their production. In consequence, the high titer of specific antibodies, both cellular and humoral, no longer exists, thus leading ultimately to a normergic state of sensitiveness (for further details, see p. 92).

It is interesting to note that deallergization therapy not infrequently results in a reduction of the hypersensitiveness to other allergens and also definitely increases the general resistance of the organism. Thus, if, in a given case, egg is the principal allergen, and flour and spinach are weaker allergens, skeptophylactic treatment of the egg hypersensitiveness will frequently diminish the allergy to the other two foods. Moreover, a general increase in resistance is often observed—manifested, for example, by a decreased susceptibility to upper respiratory infections.

The methods of specific deallergization can be subdivided as follows: spontaneous deallergization, specific shock therapy, and specific skeptophylactic methods.

1 SPONTANEOUS DEALLERGIZATION

In cases in which the hypersensitiveness has existed for only a short time, mere avoid

*Malva has demonstrated that injections of sulfur in oily solutions produce the same biologic reactions as injections of foreign proteins.

ance of the allergen may suffice to bring on complete deallergization. This almost always takes place following passive allergization of human beings and animals, as by the transiusion of antibody-containing blood, or locally, as in the Prausnitz-Kuestner test, for instance. In all such cases the deallergization results from the disappearance or destruction of the passively introduced antibodies. A further example is the deallergization of patients with mild food allergy by means of daily ingestions of small quantities of the given food. This is often seen in children hypersensitive to milk, eggs, and other foods. Equally good results can be obtained in mild contact dermatitis of allergic origin by permitting the patient to continue the work in which he is exposed to the known causative allergen.

2. SPECIFIC SHOCK THERAPY

The rationale of specific shock therapy is discussed on page 93. One technic is to overload the organism with a massive dose of the antigen, thereby producing an anaphylactic shock. While this procedure usually results in permanent deallergization, it must be strictly avoided because of the extreme danger involved. In cases of extraordinary hypersensitiveness, however, it sometimes unintentionally occurs that a reasonable dose of the antigen produces a severe constitutional reaction which will frequently be followed by a state of complete insensitiveness often lasting for months.

Even oral administration of shock doses of the antigen may be followed by temporary deallergization. Thus, Shelmire⁵⁷ employed a single oral dose of from 5 to 30 drops of a 1:25 dilution of poison ivy oleoresin in corn oil, in gelatin capsules. He found that rather severe signs of intolerance were evoked in patients with previous histories of ivy dermatitis and with positive reactions to patch tests with ivy oleoresin. When the same dose was given one week after the symptoms had disappeared, there was no reaction, and the patch tests showed a marked decrease in cutaneous sensitivity. However, lasting insensitiveness to contact with poison ivy did not follow these peroral shock doses.

3. SPECIFIC SKEPTOPHYLACTIC METHODS

Since spontaneous deallergization cannot

be relied upon and specific shock therapy is considered dangerous, the methods referred to here as "specific skeptophylaxis" are recommended as the treatment of choice. They are based on the animal experiments of Besredka.⁵⁸ Administration of a small quantity of the antigen will protect the animal against anaphylactic death from a lethal shock dose of antigen, provided that, for the route employed, the proper time relationship and dosage are maintained. According to Besredka's fundamental studies, all routes of administration (intravenous, intraperitoneal, subcutaneous, intraspinal, intracerebral, oral, rectal) are feasible in experimental animals. In human beings, however, only oral and subcutaneous skeptophylaxis are recommended as safe and effective.

In the following pages the more important methods based on skeptophylactic principles are discussed. The majority of students in this field classify them under the heading of hyposensitization. The experimental and theoretic reasons that induce the authors to include them under deallergization will be found on page 92.

Besredka called this type of protection *anti-anaphylaxis* to designate the state of insensitiveness achieved in the specific manner described. The term *skeptophylaxis* (from the Greek *σκηπτος*, "stroke of lightning," and *φύλαξις*, "protection"*) was given to this method by Lambert and his associates and has been more or less generally accepted.

Skeptophylactic treatment results in a prompt temporary protection against anaphylactic shock or other allergic manifestations, and further, if the treatment is continued, in the permanent disappearance of the allergic state as a result of the loss of cellular antibodies.

This concept of the mechanism of skeptophylaxis is not shared by Besredka, the brilliant discoverer of the method. He is of the opinion that the process involved is not one of immunity, but only of detoxification. However, the results of Weil and Coca's

⁵⁸ BESREDKA, A. *Anaphylaxis and Anti-Anaphylaxis and Their Experimental Foundations*. St. Louis, Mosby, 1919.

* In this connection, we must call attention to the erroneous etymologic derivation given in the medical dictionaries *σκηπτικός* "doubtful."

experiments (p 94) and of the senior author's lung perfusion tests in skephotophylactically protected animals demonstrating the loss of specific cellular antibodies (i.e., deallergization), prove that a true antigen antibody mechanism is implicated

a) PARENTERAL ROUTES

Skephotophylactic methods utilizing the subcutaneous route have long been employed in treatment of hypersensitiveness to serum. For example, first a minute quantity (0.1 cc of a 1:10 dilution) is injected intracutaneously, fifteen minutes later, 0.1 cc of undiluted serum is given subcutaneously (if no untoward reactions occur), then, at intervals of ten minutes, successive subcutaneous injections are administered in steadily increasing doses—0.5 cc, 1 cc, 2 cc, 5 cc, 10 cc—until finally the necessary amount of serum has been injected subcutaneously.

Intravenous skephotophylactic methods, on the other hand, have not, as yet, received any practical acceptance, despite the numerous modifications that have been suggested. This is because of the possible danger of severe or fatal constitutional reactions following injection of even a moderate dose. The method has as its aim the gradual neutralization of the antibodies by administration of the antigen in subthreshold doses, insufficient to elicit a shock. This is done by injecting successive doses of slowly increasing concentrations at intervals of only several hours. Attempts have been made to minimize the danger by employing very high dilutions of the antigen and by giving the injections at a very slow rate. Sicard, Paraf, and Forestier inject a small quantity into an arm vein below a tourniquet, thus preventing the antigen from entering the circulation too rapidly, after five minutes the tourniquet is gradually loosened, with the result that the injected substance now enters the general circulation slowly and in high dilution, ten minutes later the full therapeutic dose may be injected.

During the past few years many attempts have been made to achieve insensitiveness within one or two days by means of subcutaneous or intravenous injections given at very brief intervals. Freeman,⁸⁰⁴ Waldbott

and Ascher,⁸⁰⁵ Bray,⁷⁹ and others have reported excellent results in hay fever, Freeman,⁸⁰⁴ in asthmas due to fish, horses and molds, Hart,⁸⁰⁶ in a case of asthma attributed to cats. Ulrich, Hooker, and Smith,⁸⁰⁷ Corcoran⁸⁰⁸ and others, in the treatment of hypersensitiveness to insulin. These authors have all stressed the very rapid attainment of insensitiveness.

The technic of this method—called rush desensitization^{79*} by Freeman—is as follows. For two to four days ("day" is understood to mean fourteen hours) doses of the antigen are injected, each 10 to 30 per cent larger than its predecessor, first at intervals of fifteen to twenty minutes, then of two, four, and finally six hours. The first dose is to be regarded as a tentative one depending on the patient's reaction to the skin test. If this or any of the subsequent injections give rise to an unduly strong local or general reaction, the next dose is not increased, but should be the same or even smaller. When the maximum dose has been reached, it is repeated at intervals of ten days for a long period of time. After a few days of treatment, the patient will be insensitive to the point of being able, with impunity, to return to the occupation (or home) that he was formerly unable to tolerate. Waldbott and Ascher reported that, after four to seven days, the maximum dose of pollen (8,000 units) could be given. And Corcoran in one day of treatment succeeded in achieving tolerance to 40 units of insulin in a patient who had previously been unable to take 0.2 units. The writers have employed this method in a few cases of insulin allergy with very satisfactory results. The scale of dosage in cases of average hypersensitiveness will be found in Table 26.

The same method can also be employed in drug allergies. Thus, the senior author was able to prevent nitritoid crisis from arsphenamine, for example, by a similar technic. First, an intravenous injection of 0.005 Gm of neoarsphenamine is given, after five minutes,

⁸⁰⁴ WALDBOTT G L and ASCHER M S. *J Allergy* 6: 93, 1934.

⁸⁰⁵ HART P D A. *Proc Roy Soc Med* 23: 265, 1930.

⁸⁰⁷ ULRICH H, HOOKER, S B and SMITH H H. *New England J Med* 224: 522, 1939.

⁸⁰⁸ CORCORAN A C. *Am J Med Sci* 196: 339, 1918.

* While the term rush desensitization as coined by Freeman is used here, the method is actually based on skephotophylactic principles and is therefore really a form of deallergization.

a dose of 0.015 Gm., followed five minutes later by 0.05 Gm., and after another two minutes by 0.10 Gm. If the patient tolerates these doses well, this procedure is continued on successive days with very cautiously increased

For the present, at least, the "rush" methods are to be employed only in well-equipped hospitals and under the supervision of experienced physicians. The danger inherent in them must always be borne in mind. Ac-

TABLE 26—Scheme of "Rush Desensitization" in Insulin Hypersensitiveness

Time	Route	Units of Insulin	Tests and Nutrition
FIRST DAY			
9:00 A.M.	intradermal	0.1	fasting blood sugar; breakfast
9:20		0.2	
9:40		0.4	
10:00		0.8	
10:20	subcutaneous	0.2	lunch
10:40		0.4	
11:00		0.8	
11:20		1.0	
11:40		2.0	
12:00 M.		4.0	
12:20 P.M.		8.0	
12:40		10.0	
1:00	intravenous	0.3	1 unit intradermally as skin test, blood sugar
1:20		0.6	
1:40		1.0	
2:00		2.0	
2:20		4.0	glucose intravenously, if necessary
2:40		8.0	
3:00		10.0	
3:00		10.0	
SECOND DAY			
9:00 A.M.	intradermal	1.0	fasting blood sugar, breakfast
9:20	subcutaneous	1.0	1 unit intradermally as skin test, blood sugar
9:40		2.0	
10:00		4.0	
10:20		10.0	
10:40	intravenous	20.0	30 Gm. carbohydrates by mouth glucose intravenously if necessary lunch 1 unit intradermally as skin test, blood sugar, followed by 30 Gm. carbohydrates by mouth
11:00		1.0	
11:20		2.0	
11:40		4.0	
12:00 M.		10.0	
12:20 P.M.		20.0	

doses. However, if any one of the injections causes any kind of reaction whatever, the treatment is stopped for that day, and is resumed after a day or two with a smaller and very slowly increasing dosage. In order to avoid repeated introduction of the needle, we use one that is equipped with a stylet and that can stay in the vein throughout.

According to our own observations, as well as those of other investigators, the danger is decreased to a certain extent when small amounts of epinephrine (0.05 to 0.1 cc.) are mixed with the antigen before injection.

In the management of cases of specific allergic dermatitis, asthma, and rhinopathy, one of us has employed the skeptophylactic

principle in a modified technic two injections were given daily—a very weak dose in the morning followed six hours later by a considerably stronger one. The following case histories will illustrate the procedure.

Two female workers in the nickel industry who had been suffering from widespread dermatitis for months had a definite eczematous reaction to patch tests with even a 1:1,000,000 dilution of nickel sulfate. Deallergization was achieved by the daily administration of two subcutaneous injections of nickel sulfate solutions. The first was 0.1 cc of a 1:1,000,000 dilution while the second was of 1:1,000,000 strength. By gradually increasing the concentration we arrived at a strength (1:100) that induced strong local and focal reactions. Within seventy-two hours these had disappeared. When therapy was resumed even with a cautious increase in the dosage reactions appeared that necessitated repetition of given strengths. Treatment was stopped when a 1:700 dilution in the morning and a 1:70 dilution in the afternoon was reached. At this time a patch test with an 11 per cent nickel sulfate solution evoked only a very mild local reaction. Almost every normal skin will show some response to this concentration. The patients then returned to work and were able to continue at it with impunity, provided they did not put their hands directly into the nickel bath. Follow-up ten months later revealed that they responded with only a trifling reaction to an 11 per cent nickel sulfate patch test.

In individuals suffering from baker's rhinopathy or baker's asthma a scratch test is made to determine the smallest dose of flour that will elicit a slight reaction. Thereafter the patient receives a subcutaneous injection of 0.1 cc of one-tenth the strength of the test solution (e.g. 0.1 cc of a 0.001 per cent solution) and another injection six hours later of the same quantity of the flour solution in a concentration ten times stronger. Proceeding in this way the strength of the doses is gradually increased until the maximum dose (generally 1 cc of a 5 per cent solution) is reached which is within about six weeks. During the course of treatment the patient must carefully avoid all contact with the allergen. By means of this method a number of bakers were entirely cured of rhinopathy and asthma.

b) ORAL ROUTE

The oral skeptophylactic method has proved of great value in the treatment of both drug and food allergies.

Thus Heran and Saint Girons⁵⁰ successfully employed measures amounting to oral deallergization in patients with hypersensitiveness to aspirin and quinine, the senior author in cases of hypersensitiveness to iodine, quinine and other drugs.

The following case history is presented for the purpose of illustrating the technic employed.

A woman with asthma had been taking 0.5 Gm of potassium iodide for months with good symptomatic results. She eventually acquired a vesiculopapular

TABLE 27—*Scheme of Oral Deallergization with Potassium Iodide*

Dose No	1st Day Gm	2d Day Gm	3d Day Gm
1	0.005	0.01	0.1
2	0.01	0.015	0.118
3	0.02	0.03	0.136
4	0.03	0.045	0.154
5	0.04	0.06	0.172
6	0.05	0.075	0.19
7	0.06	0.09	0.208
8	0.07	0.105	0.226
9	0.08	0.13	0.244
10	0.09	0.145	0.262
11	0.10	0.16	0.28
12	0.11	0.175	0.298
13	0.12	0.19	0.316
14	0.13	0.205	0.334
15	0.14	0.22	0.352
16	0.15	0.235	0.37
Total	1.205	1.890	3.760

exanthem due to hypersensitiveness to iodine. Efforts at oral hyposensitization resulted in new and severe skin manifestations. We therefore instituted a skeptophylactic technic administering as the first dose on the first day 0.005 Gm of potassium iodide. Every forty-five minutes this dose was increased by 0.01 Gm until sixteen doses had been administered. The peak dose on the first day was 0.15 Gm and the total amount given on that day was 1.205 Gm. On the second day we began with 0.01 Gm; the dose was increased each time by 0.015 Gm and a total of 1.89 Gm was thus administered without untoward effect. On the third day we began with 0.1 Gm and increased the dose by 0.018 Gm administering a total of 3.76 Gm on that day (see Table 27). From that point on 0.5 Gm of potassium iodide was given three times daily.

It is clear that a similar basic principle is involved in the methods in which infinitesimal

quantities of an allergenic food (e.g. milk, egg) are administered by mouth forty-five minutes before that food is eaten.

But even minute amounts of allergenic foods may elicit the most alarming symptoms.* For this reason Pagniez and Vallery-Radot⁸¹² modified the procedure by giving the patients not the natural food proteins, but ordinary commercial meat peptone, forty-five minutes before eating the allergenic food. These authors reported satisfactory results with this method in cases of urticaria, strophulus, and angioneurotic edema. Auld and Luithlen, however, were unable fully to confirm these findings. Auld,⁸¹³ therefore, prepared two kinds of peptones, one of animal and one of vegetable origin, and combined them when necessary. It was Luithlen,⁸¹⁴ however, who first recognized the importance of employing a strictly species-specific digestion product for effective skeptophylactic action. Thus, a strictly specific allergy to cow's milk cannot be controlled with meat peptone. Luithlen logically prepared a variety of species-specific animal and vegetable peptones for therapeutic use.

Moreover, he had preparations made in which the digestion of the protein was carried beyond the stage of production of proteoses, while still retaining the specificity of the protein from which it was derived. He found this necessary because the commercial "peptones" (Armour, Witte), as Auld⁸¹¹ had pointed out, consisted largely of proteoses and only to a small extent of peptones and simpler nitrogen compounds. Luithlen, however, was not able to perform the necessary immunologic and clinical studies with his peptones, since he died shortly afterward.

After some years of experimental work, Urbach⁸¹⁵ presented proof that in cases of

specific food protein allergy only the specific protein derivatives as described above, administered by mouth, have a skeptophylactic effect and consequently will give rise to permanent deallergization. Furthermore, he demonstrated that these preparations can be used for diagnostic identification of the allergens (see p. 190).

(1) *Propeptan Therapy*

Before presenting animal experiments, we might explain the term propeptan.⁸¹⁶ Propeptans are food digests derived from the individual foods by means of prolonged digestion with hydrochloric acid and pepsin, followed by slight additional digestion with trypsin. They are composed of proteoses, peptones, subpeptones, simple peptides, and amino acids. While their allergizing effect is attenuated by this chemical change, they still retain the specificity of the corresponding proteins. Unlike the commercial peptones, the propeptans do not contain natural protein, as indicated by the absence of acid precipitated nitrogen. Full details of the chemical composition of the propeptans were presented by Urbach, Jaggard, and Crisman.⁸¹⁷

The senior author has shown that a guinea pig highly allergized to egg white can be protected against usually lethal anaphylactic shock by a preliminary injection or feeding of chicken egg propeptan, while other propeptans and even chicken meat propeptans are totally inefficacious. The strict specificity of the propeptans can also be demonstrated by means of the Schultz-Dale test: the uterus of a guinea pig allergized to hen egg propeptan contracts after addition of only this propeptan and not on addition of a propeptan derived from any tissue of the hen (Urbach and Kitamura⁸¹⁸).

In view of the fact that the uterus of a guinea pig allergized to egg white does not react to the addition of egg propeptan in the Schultz-Dale test, W. Jadassohn and Schaaf⁸¹⁹ have concluded that the propeptans are not species-specific. Urbach and Wolfram, on the other hand, have demonstrated that this test cannot properly serve to answer this question, because

* The following representative cases may serve as examples severe general manifestations in an infant following oral administration of 5 drops of milk (Cathala, Ducas, and Netter⁸¹²), urticaria after 1 drop of milk, and edema of the lungs simulating asthma after several drops (Hopkins and Kesten⁸¹³), dyspnea from a 1:100,000 dilution of egg white (Adelsberger and Munter).

⁸¹² CATHALA, J., DUCAS, P., and NETTER, A. *Bull. Soc. de pediat. de Paris* 31: 224, 1933.

⁸¹³ HOPKINS, J. G., and KESTEN, B. M. *Eighth Internat. Dermat. Congr., Copenhagen, 1930*, p. 602.

⁸¹⁴ PAGNIEZ, P., and VALLERY-RADOT, P. *Presse med.* 24: 529, 1916.

⁸¹⁵ AULD, A. G. *Brit. M. J.* 1: 695, 1921.

⁸¹⁶ *Ibid.* 2: 49, 1918.

⁸¹⁷ URBACH, E. *Klin. Wchnschr.* 9: 2346, 1930; *Wien. klin. Wchnschr.* 43: 503, 1930.

⁸¹⁸ *Ibid.* *Med. Klin.* 27: 1125, 1909, 1933.

⁸¹⁹ JADASSOHN, E., JAGGARD, G., and CRISMAN, D. W. *Ann. Allergy* 2: 424, 1944.

⁸²⁰ JADASSOHN, W., and SCHAFF, F. *Klin. Wchnschr.* 14: 793, 1935.

the specificity of this procedure is so high that positive results can be achieved only with antigens that are chemically completely identical, and not with antigens that are biologically equivalent but chemically somewhat different. The immune-biologic relationship that exists between a protein and its derivatives—called “species specificity”—cannot, therefore, be demonstrated by the Schultz Dale method. But it can, on the other hand, be demonstrated by the following skeptophylactic animal experiments.

action. By means of the Schultz Dale technic, Urbach et al.⁸¹⁹ were able to show that the uterus of an animal sensitized to egg propeptan is specifically hypersensitive in that it reacts neither to egg white from which the egg propeptan is derived, nor to the propeptan prepared from muscle tissue (chicken meat propeptan), nor of course to other propeptans such as milk propeptan, but it reacts exclusively to the substance with which it was sensitized—egg propeptan (FIG 76). The same type specificity can be demonstrated

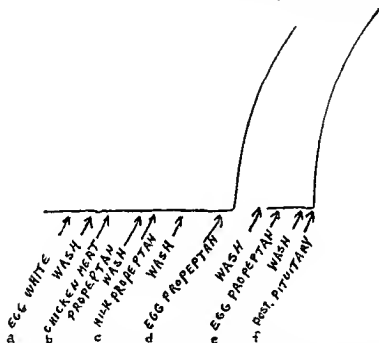


FIG 76 SPECIFICITY OF PROPEPTAN REACTION

Uterine reaction (Schultz Dale test) of guinea pig allergized to egg propeptan. No reaction on addition of egg white (a) chicken meat propeptan (b) or milk propeptan (c) but violent reaction to addition of egg propeptan (d). No response to second addition of egg propeptan (e) proving first reaction to be specific for egg propeptan. Posterior pituitary extract added (f) as check on viability of uterus.

When a guinea pig allergized to egg white, for example, is given a small amount of egg white intravenously three weeks later, it promptly dies of anaphylactic shock. If, however, the shock dose is preceded by four intravenous injections of egg white propeptan, in doses of 1 mg, 5 mg, 10 mg, and 20 mg, respectively, at intervals of five minutes, the animal has only slight transitory symptoms.

Since the question of the strict specificity of the propeptans has theoretic as well as great practical significance, it seems desirable to submit the experimental evidence regarding

this point, as well as their skeptophylactic in the lung perfusion test. These findings are paralleled by clinical observations in numerous cases showing that protection is afforded only by the specific propeptan derived from the particular food evoking the hypersensitivity.

In order to prove that this therapy is based on the skeptophylactically protective action of type-specific propeptans, Urbach, Jaggard, and Crisman^{819, 820} demonstrated in an ex-

⁸¹⁹ URBACH E, JAGGARD G and CRISMAN D W. *Ann Allergy* 3: 172 1945.

⁸²⁰ *Idem* *ibid* 3: 287 1945.

tensive series of experiments that the appropriate oral, intravenous, or subcutaneous administration of egg propeptan to animals previously sensitized to egg white is capable of preventing otherwise certain anaphylactic death from anaphylactic shock. Moreover the organs of such protected and surviving animals will fail to react to the Schultz-Dale test and to the lung perfusion test, indicating the absence of cellular antibodies, and hence a true deallergization. In addition, it can be shown that in guinea pigs orally allergized to food proteins and presenting allergic manifestations after the oral administration of the particular food, symptoms can be inhibited by means of food propeptans given by mouth. In other words, the animals are capable of tolerating oral shock doses of food proteins if pre-treated with specific food propeptans. The absence of tissue antibodies is evidenced by negative lung perfusion tests. As shown by experimental work,^{819, 820} food propeptans act by inducing microshocks producing at first partial and temporary, and later complete and lasting satiation of the antibodies, thus leading to deallergization.

Despite the chemical differences between proteins and propeptans, as well as the results of Schultz-Dale tests, the fact that skeptophylactic protection can be afforded only by biologically closely related agents proves that these derivatives have retained their species specificity. Nadel⁸²¹ undertook an exhaustive experimental investigation of this controversial question and came to the conclusion that the oral administration of partially digested protein for skeptophylactic purposes, as in propeptan therapy, has genuine theoretic and experimental foundation.

Rowe,⁷⁴⁰ on the other hand, found that animals sensitized with a given food can be shocked with intracardiac injections of the specific peptone, and claimed that traces of the original protein were still present. This only shows that Rowe worked with a preparation that was insufficiently digested; for similar experiments with the original propeptan (Urbach and Kitamura¹⁸⁵) yielded entirely negative results. Moreover, W. Jadassohn,⁸¹⁹ as well as the senior author, was unable,

despite the most exacting methods (Schultz-Dale technic) to find any traces of the original proteins in the propeptans.

Vaughan⁸¹ raised three pertinent questions:

(1) *Can a protein be partially digested toward the peptone stage and still remain partially antigenic?* Surely, for it is not infrequently observed that, in cases with a high degree of hypersensitiveness, as small a dose as for example 0.1 Gm. of egg propeptan can elicit allergic manifestations, and that these will cease to appear only after the patient has been systematically deallergized with 0.01 or 0.001 Gm. of egg propeptan.

(2) *Will such a modified antigen protect against exposure to the unaltered allergen forty-five minutes later?* Yes, for at about this time the organism is in a so-called negative phase ("anti-anaphylactic stage," according to Besredka). During this stage—for reasons we do not fully understand—the available antibodies do not function as such, and the antigen therefore cannot enter into an antigen-antibody reaction.

(3) *Will repeated administration of this altered allergen, synchronously with repeated contact with the whole allergen, permanently desensitize (deallergize) an individual within thirty days?* Numerous authors (Bauer, Brandt; Chajes; von Eiselsberg, von Eiselsberg and Kauders; Freund; Hauramoto; Hecht, Hermann, von Hoesslin, Hopkins, Waters, and Kesten; Kaemmerer; Kauders, Kitamura, Markin, Rehfuess, Reiss, Rusten, Senn; Shay-Singer; Schmidt, Schreiber; Schreus; Ulrich, and others) report lasting results obtained with this method within two to three weeks of treatment. Others, however, (including Bray, Rowe, Vaughan, C. White), had no success with this method. This difference in results achieved may be explained by the fact that the first group of authors employed the original propeptans, while the latter employed their own preparations.

Propeptan therapy is our method of choice for the control of every type of hypersensitiveness to food proteins, irrespective of the clinical manifestations of the condition, such as asthma, rhinopathy, urticaria, or colitis.

Finally, it is to be noted that the same principle of skeptophylaxis is the basis of the treatment of hay fever with pollen propeptan, provided the given allergen is administered three to four times daily.

⁸¹⁹ NADL, A.; Zisch, J. d. ges. exper. Med. 102: 606, 1938, 103: 446, 1938, 104: 50, 1939.

(2) *Technic of Propeptan Therapy*

After the identity of the food allergen or allergens has been established (see p 186), deallergization is undertaken in the following manner. The patient is told to eat once daily those foods revealed to be responsible, and at the same time is given the corresponding species-specific propeptans, each capsule contains 0.1 Gm of propeptan plus 0.01 Gm of glycyrrhiza*. These capsules should be taken exactly three quarters of an hour before each meal. It is utterly useless to administer the propeptans on a full or partly full stomach, therefore, there must always be an interval of at least four hours between meals (three hours in the case of small children). During these intervals, nothing except small quantities of water or perhaps some sugar may be consumed. In cases in which 1 capsule is not sufficient to control the symptoms, or if larger quantities of the given food are eaten, 2 or more capsules should be taken at each dose for a few days. In infants propeptans without glycyrrhiza should be used.

The following case history will present an example of how these principles are applied in practice. It must be stressed that in each case some variation in the doses of propeptan required, the amount of food tolerated, and the duration of treatment will be encountered.

A 16-month old boy had had recurrent asthma and vomiting from the age of 2 months on. Symptoms ceased when cow's milk was eliminated from the diet. There was no allergy in the family. Administration of half a glass of milk produced vomiting in thirty minutes followed by marked wheezing for several hours. Milk propeptan and milk were administered as shown in Table 28. It will be seen that at the end of 2 weeks the patient could tolerate a half pint of milk without pre-treatment.

In cases of hypersensitiveness to several foods, all the corresponding propeptans must be taken—as, for example, milk, egg, and beef propeptans when hypersensitiveness to these three foodstuffs has been discovered. Table 29 illustrates how this is done.

When a patient is so extremely hypersensitive that even 1 capsule of propeptan elicits clinical manifestations, the propeptan must be administered, to start with, in doses of

0.01 Gm, or, in exceptional cases, of 0.001 Gm diluted with sugar. A correspondingly small amount of the given foodstuff (for example, 1 to 5 Gm) is to be given the patient forty five minutes later.

The achievement of complete deallergization takes longer in some cases than in others. The average period of treatment is somewhere between two and four weeks. As already mentioned, the procedure in practice consists in giving the patient all the nontolerated food items twice daily for a period of fourteen

TABLE 28—Outline of Propeptan Therapy in a Case of Milk Hypersensitiveness

Day	Milk Propeptan Tablets (0.1 Gm each)	Milk (Cc) (45 min later)	Symptoms
1st	1	10	slight wheezing diarrhea
2d	2	10	very slight wheezing
3d	3	10	none
4th	3	20	none
5th	3	30	none
6th	3	50	slight diarrhea
7th	3	50	none
8th	3	75	none
9th	3	100	none
10th	3	150	none
11th	3	200	none
12th	2	200	none
13th	1	200	none
14th	½	200	none
15th	0	200	none
Further, daily	0	250	

days—with preprandial administration of the proper propeptans. During this period no attempts should be made to determine whether or not the hypersensitiveness has decreased or disappeared. But when the patient has been completely and constantly free from objective and subjective symptoms for fourteen days, the number of capsules is gradually reduced to zero. If there was hypersensitiveness to several foodstuffs, not all the types of propeptans are stopped at one time, but first the propeptans of one type, and then, if no manifestations appear, the propeptans of a second, then those of a third type, and so on. The

* A saponin derived from glycyrrhiza root. This is added to enhance the intestinal resorption (see p 47).

treatment may be terminated only when the food or foods formerly not tolerated are taken with perfect impunity without preceding administration of propeptans. If allergic manifestations appear—as rarely happens—another fourteen-day period of propeptan treatment is indicated. It is absolutely essential, furthermore, that for many weeks after the termination of treatment the patient must take all the previously nontolerated foods, naturally without propeptans, at least once daily in order to maintain his state of deallergization.

before the meal time. The diet may consist, at the patient's choice, of any of the thirteen food items listed above. Since these capsules are inefficacious unless taken on an empty stomach, intervals of at least four hours must be maintained between meals (in the case of small children, three hours). During these intervals, no food or liquid is to be taken except a small amount of water or a few sips of sugar water if desired. If the symptoms are not relieved, it is sometimes necessary to give a larger number of polypropeptan capsules before each meal.

TABLE 29.—Outline of Propeptan Therapy in a Case of Hypersensitiveness to Milk, Beef, and Egg

Time	Propeptans (2 of each)	Time	Diet
7:15 A.M.	milk, egg	8 A.M.	fruit juice, cereal (with milk), hard-boiled egg, coffee with cream, toast, butter
11:15 A.M.	beef, milk	12 M.	roast beef, vegetable, ice cream
5:15 P.M.	egg, milk	6 P.M.	omelette, vegetables, chocolate milk shake

(3) Polypropeptan Therapy

In order to simplify the technic for the patient and to reduce the cost, a mixed propeptan, called "polypropeptan," has been prepared. Each capsule of this polypropeptan contains 0.05 Gm. of 13 different species-specific propeptans (beef, chicken, egg white, milk, wheat, rye, oat, potato, spinach, pea, string bean, tomato, apple) plus 0.03 Gm. of glycyrhiza.*

The chief advantage of polypropeptan therapy over that with individual specific propeptans is that by taking 2 or 3 of these capsules the patient is permitted to eat anything within the limits of the thirteen food items; and he is thus freed from worrying about having eaten something against which he was not, perhaps, duly protected.

In practice, the polypropeptan treatment proceeds in the following manner. When there is good reason to suspect the presence of a food allergy in a given case, the identity of the possible allergen need not necessarily be ascertained, but the patient is given 2 or 3 polypropeptan capsules exactly forty-five minutes

It takes longer in some cases than in others to achieve permanent deallergization. The average period of treatment is three weeks. The patient is therefore instructed to adhere meticulously to the propeptan routine for about this time. When completely free from all manifestations, he may be permitted gradually to decrease the dose to 1 capsule for a few days. Then he may omit the polypropeptan before lighter meals (e.g., breakfast or a small lunch), until, finally, he may be permitted to take his regular meals (restricted to any of the thirteen food items) without previously taking his capsules. If he remains asymptomatic, he is then to add a new food to his diet every second day. This is necessary because foods other than the thirteen contained in his diet may also be allergens.

In order to arrive at a more varied diet more rapidly, the following procedure may be employed. If the patient is free from manifestations after one or two weeks of polypropeptan treatment, he may add one new food every other day to his diet while still taking the polypropeptans. Should allergic phenomena appear, it means that the most recently added food is an allergen. This can

* See footnote, p. 220

be dealt with either by elimination from the diet or by having the patient take the corresponding specific propeptan (e.g., orange propeptan) in addition to the polypropeptan.

(4) *Sources of Error in Propeptan Therapy*

Not every failure of propeptan therapy should immediately be blamed on the method itself, it may be due to other factors.

(1) The case may be not one of food allergy. This question can be decided by placing the patient on a strict sugar diet (consisting only of approximately 300 Gm of sugar per day, and water) for 2 days. Only if there is rapid improvement can the condition be considered as a case of food allergy.

(2) While the case may be one of food hypersensitiveness, this need not necessarily be in relation to proteins. For it should be remembered that propeptans are effective only in allergies to nutritive proteins, and are therefore useless in cases of hypersensitiveness to carbohydrates, fats, acids, or salts (see p. 295 for methods of determining whether a protein or nonprotein food is the allergen in a given case).

(3) Some patients present a combination of protein and nonprotein food allergies. Thus, a patient with severe lichen urticatus of ten years' duration was definitely improved by propeptan therapy. However, after every highly spiced or salted meal, relapses were noted. Mere elimination of salt and spices from the diet mitigated the itching but did not suffice to abolish it. However, the combined treatment resulted in a permanent cure within four weeks.

(4) It is essential that the various predisposing factors (see p. 60) be searched for and, if possible, corrected. Thus, in cases of hypochlorhydria or achlorhydria the administration of hydrochloric acid and pepsin must accompany the propeptan treatment. Either therapeutic measure alone will not be successful. Similarly, in the case of patients with chronic enteritis, an appropriate diet is necessary along with the specific propeptans. Furthermore, foci of infection in teeth, tonsils and elsewhere must be considered, since not infrequently propeptan therapy will remain ineffective until these are eliminated.

(5) It must be remembered that in some cases many times the usual dose of propeptan must be given in order to achieve cure. Thus one of us reported 3 cases, one of asthma, another of laryngeal edema and gastro-intestinal symptoms, and a third with angio-neurotic edema due to food hypersensitiveness (egg, pea). In each case large doses, from 0.5 to 1 Gm, of egg or pea propeptan (i.e., 5 to 10 capsules) had to be given before each meal in order to obtain freedom from symptoms. These large doses may soon be reduced (by 2 capsules daily), so that within two to three weeks a point is reached at which 1 capsule per meal is sufficient.

(6) On the other hand, in rare cases of extraordinary hypersensitiveness to a given protein, ingestion of even a one-half dose of propeptan may elicit allergic manifestations. In this contingency the treatment must be initiated with 0.01 to 0.001 Gm. In one case of extreme hypersensitiveness to fish, it was necessary to begin with 0.000001 Gm of propeptan mixed with sugar.

(7) Finally, it should be borne in mind that a state of insensitiveness only newly achieved by propeptan therapy may be annulled by ingestion of large quantities of the allergenic food to which the patient had been rendered tolerant.

Furthermore, reallergization may take place as the result of intercurrent infection, such as a cold, or gastro-intestinal irritation due to alcohol, acute enteritis, excessive use of laxatives, or ingestion of very cold foods (iced drinks). The newly acquired allergization need not be to the same foods but may be to other ingestants, including drugs taken by mouth.

Finally, it should be stressed that propeptan therapy must always be meticulously carried out. We have found it useful, therefore, to give the patient a ruled blank, which he is asked to fill out and bring in at each visit, we are thus able to check and correct any mistakes he may have made. In our experience errors are almost inevitable, especially in the beginning, despite the most painstaking explanations and instructions. Moreover, the physician should always keep in mind the possibility of minute quantities of certain forbidden foods being consumed by the patient.

without his knowledge—such as traces of egg in the crust of rolls, the milk contained in ice cream or chocolate candy, meat stocks in “vegetable” soups, wheat flour in “rye” bread, or flour in gravies. Such examples of overlooked proteins constitute a common source of error and confusion, but this should not be charged against the method.

From these few examples it will be seen that complete understanding and scrupulous attention to details are essential to the proper supervision of a course of propeptan therapy.

F. HETEROSPECIFIC DEALLERGIZATION

The procedure of overloading the organism with specific antigen has been discussed above (p. 93). The same thing can also be done with heterospecific antigens. The efficacy of this latter method is explained by the fact that after severe anaphylactic shock—regardless of the nature of the anaphylactogen eliciting it—the organism's entire supply of antibodies is either satiated or in some other manner rendered incapable of reacting. On the basis of this observation, intentional elicitation of shock by means of serum or peptone has been recommended by several authors (Coke, in the treatment of resistant asthma, Kalk in mucous colitis). We hasten to add, however, that we emphatically advise against these measures, since at present there is no means of gauging the dosage so as to prevent endangering the patient's life.

G. SYMPTOMATIC THERAPY

There are a certain number of cases in which the causative allergen cannot be identified or in which for one reason or another the various methods of hyposensitization or deallergization are not sufficiently effective. In such instances symptomatic therapy must be employed. All of the many methods that have been devised for this purpose can be traced back to two basic mechanisms, both of which are nonspecific in nature and reduce the reactivity of the shock structure: (a) measures capable of decreasing the hypersensitiveness, such as general hygiene, diet, drugs, and (b) measures to raise the threshold to stimulation, for example by habituation or psychotherapy.

1. GENERAL HYGIENE

As noted in some detail earlier, the current economic and social upheavals, and the general unrest of the population, constitute one of the outstanding predisposing factors in the pathogenesis of hypersensitivities. Although the physician cannot, of course, do anything about the world's affairs in general, he must make every effort to help the individual patient regain his psychologic equilibrium. The physician must also see to it that the patient does not overexert himself mentally or physically, and that he gets sufficient rest and peace, as well as a reasonable amount of relaxation and diversion from his worries by engaging in some sport, putting about in his garden, or following the hobby of his choice. Vacations—and particularly regular weekends or holidays—are especially beneficial.

Sun baths, or, if this is not possible, prolonged exposure of the body to fresh air and light, will serve to strengthen and harden the patient. They are also of value because they stimulate the physiologic functions of the skin, which plays such an important part in the defense mechanism of the body. Similar results can be obtained by the use of cold and hot water for washing, bathing, and packs, by sweat-inducing procedures, steam baths, massages, and exercise. Adequate and natural evacuation is important. Furthermore, the patient must be taught to eat slowly and masticate thoroughly.

A painstaking search should be made for possible foci of infection; if feasible, these should be eliminated. Careful study of the gastro-intestinal tract will often be far more helpful than the patient's history in discovering digestive diseases or functional disturbances. In suitable cases, stool cultures should be made, since pathologic intestinal flora not infrequently constitute a focus of infection.

2. DIET

The city dweller's usual diet—rich in proteins, salt, and spices, on the one hand, and poor in calcium, vitamins, and roughage on the other—tends to support and maintain allergization. This point has been discussed in some detail on page 67. Furthermore, the

widespread tendency to indulge habitually—not to say excessively—in alcohol, coffee, and tobacco definitely fosters allergy

The question of diet is worthy of special attention. A single diet, for obvious reasons, cannot be prescribed for all conditions. Generally speaking, however, it is wise to recommend a diet that is poor in salt and spices, rich in fruits and vegetables, and restricted as to proteins (100 to 150 Gm of meat two or three times weekly). As to raw fruits and vegetables, the question must be decided by the condition of the teeth and gastro intestinal tract. Vitamin preparations can be very beneficial, in the form of either a multiple vitamin capsule or vitamin B complex.

Omission of table salt from the diet is often an important therapeutic measure. Cook and Stoesser⁸⁹ showed that a low sodium diet reduces the number and severity of asthmatic attacks. Rusk and Kenamore⁹⁰ reported good results with this in chronic urticaria, others in migraine.

The most important instruction to give the patient, when a low sodium diet or the so called salt free diet is prescribed, is that table salt should be banished and no salt should be used in cooking. The butter should contain no salt. Bread, cake, rolls, and cereals as ordinarily prepared are unsuitable, but may be made without salt. *Seafoods, including clams, oysters, and the like, are best omitted.* Foods that are obviously salted, like crackers, cheese, sausage, salted meats, salted fish, and most pickles, are forbidden. There is a very low sodium content in flour, cream, macaroni, sugar, potatoes, squash, parsnips, lettuce, kidney beans, tomatoes, and most vegetables. *Eggs, meat, milk, beets, Brussels sprouts, yellow corn, mushrooms, and peas* are reasonably low in sodium content and may be eaten in moderate amounts. Sodium bicarbonate should not be used. Meat contains some sodium, which can be removed by boiling if desired, the broth being discarded.

The allergic individual's diet should generally be as dry as possible—drier at any rate than his usual fare—for dehydration is often

beneficial in certain allergic conditions, such as asthma, migraine, rhinopathy.

In other allergic diseases, especially gastrointestinal allergy and urticaria, it is advisable to begin the dietary treatment with a two days' regimen during which the intake is restricted to fruit and fruit juices, particularly grape juice. It is also best at this time to prescribe a mild laxative. After this brief period of strict diet, the patient is permitted to return to a meat and salt poor diet, with restriction to raw foods or fruits one day each week. In other cases, particularly of asthma and urticaria, an acidotic diet has been found to be more beneficial. This is probably true in cases in which there is marked vagotonia. This regimen can be enhanced, according to Beckman,⁹¹ by the administration of nitrohydrochloric acid.

	Cc	
R Nitrohydrochloric acid	18 0	f5 ivss
(not diluted)		
Distilled water	q s ad 120 0	f5 iv

M Sig 1 teaspoonful in $\frac{1}{2}$ glass of water 4 times a day after meals and on retiring

Numerous investigations in the past few years have revealed a definite although non-specific anti allergic effect of glucose (30 Gm four times daily by mouth), more marked on intravenous injection (3 to 20 cc of a 20 per cent solution). Cane sugar is far less effective. In animal experiments as well, feeding of glucose or mixing of the antigen with glucose has been found to result in a definite decrease in or even complete suppression of shock. On the other hand it should be stressed that in cases of migraine the intake of sugar should be sharply reduced.

There have been various explanations as to the beneficial effect of sugar therapy. The most likely one is that of Barber and Ornel, who assume a disturbance of the 'pexic' function of the liver in allergic diseases, and therefore try to increase the glycogen content of the liver. The authors have had encouraging results with a combined insulin and carbohydrate therapy (5 to 10 units of insulin three times a day, together with large amounts of sugar).

⁸⁹ COOK M M and STOESSER A V Proc Soc Exper Biol & Med 38 636, 1938

⁹⁰ RUSK, H A and KENAMORE B D Ann Int Med 11 1838 1938

⁹¹ BECKMAN H Treatment in General Practice Philadelphia Saunders 1942

3. DRUGS

The majority of the drugs employed in the treatment of allergic diseases owe their action to their effect on the autonomic nervous system (see Table 10, p. 60). The sympathomimetic adrenergic drugs have their greatest value in the alleviation or control of acute allergic symptoms, while certain of the parasympathomimetic drugs are used in prolonged courses in an attempt to increase tolerance nonspecifically. The drugs depressing autonomic function have a more limited range of usefulness, but derivatives of ergotamine are the drugs of choice in the relief of migraine, and atropine has certain indications.

The most important drug in the symptomatic treatment of allergic diseases is without doubt *epinephrine* (adrenalin), which, by stimulating the endings of the sympathetic nerves, produces vasoconstriction and thereby counteracts the anaphylactic dilatation of the blood vessels. Epinephrine hydrochloride (0.5 to 1 cc. of a 1:1,000 solution, subcutaneously) is the sovereign remedy for anaphylactic shock. Somewhat smaller doses are effective in the vast majority of attacks of asthma, and will relieve the pruritus of acute urticaria, the swelling of angioneurotic edema, and numerous other allergic manifestations. However, epinephrine frequently causes disagreeable side effects, such as tremor, palpitation, profuse sweating, throbbing headache, vertigo, and a feeling of anxiety, restlessness, and apprehension. Garver observed four patients who had tetany immediately following moderate doses of epinephrine, and relieved by intravenous calcium. In very rare cases, even hemiplegia, the result of a ruptured cerebral vessel, has been reported. Applebaum⁴²³ has also described two instances of cerebrovascular accidents following injections of this drug, presumably due to cerebral anoxia or ischemia from vasoconstriction of the cerebral arterioles. Care must be exercised in the choice of dosage and in avoiding an inadvertent intravenous injection. Epinephrine is contra-indicated in hypertension, hyperthyroidism, arteriosclerosis, especially cerebral arteriosclerosis, organic heart disease,

angina pectoris, and certain stages of surgical shock. A way of minimizing the unpleasant effects of epinephrine is to administer it in divided doses according to the technic of Hurst and Bray. In this method, 0.1 or 0.2 cc. of 1:1,000 epinephrine hydrochloride is injected subcutaneously, and repeated every five and later every ten minutes, until a full therapeutic effect is noted, or until a total of 1 cc. has been given. In order to avoid unnecessary pain the needle is left in place.

In animal experiments, Ruskin⁴²⁴ found epinephrine ascorbate to have about twice the bronchiole dilating capacity of the hydrochloride.

Unless an immediate effect is necessary, a slow-acting epinephrine may be used, such as epinephrine in oil (Kenney⁴²⁵) or in gelatine (Spain et al.⁴²⁷), since absorption is much slower when these vehicles are employed. The usual dose is 0.5 to 1.5 cc. intramuscularly of a preparation containing 2 mg. of epinephrine base per cc. (a 1:500 suspension). It has its greatest usefulness in chronic asthma, as well as urticaria (Keeney,⁴²⁸ Thiberge⁴²⁹), angioneurotic edema, serum sickness, and certain cases of hay fever (Keeney⁴²⁹). In some circumstances, it is desirable to control the symptoms promptly by an injection of aqueous epinephrine hydrochloride, followed by an intramuscular injection of the longer-acting suspension in oil. With these preparations fewer doses need be given in twenty-four hours, with the result therefore that the side effects are usually far less distressing. However, since epinephrine in oil is a suspension rather than a true solution, absorption may be irregular, accounting for unexpected adrenalin reactions in certain cases.

In asthma a bronchial spray with 1:100 epinephrine is often highly beneficial. It is necessary for this purpose to use a special nebulizer that produces a very fine mist and contains no metal.

In this connection mention may be made of the favorable influence of the "insulin thrust" or "vegetative insulin shock" on allergic

⁴²³ APPLEBAUM, I. L.: *J. Allergy* 13: 397, 1944.

⁴²⁴ RUSKIN, E. L.: *Bull. Johns Hopkins Hosp.* 62: 227, 1938; *Am. J. M. Sc.* 1940: 815, 1939.

⁴²⁵ SPAIN, W. C., STRAUSS, M. B., and FUCHS, A. M.: *J. Allergy* 10: 209, 1939.

⁴²⁶ THIBERGE, N. F.: *M. Rec.* 152-151, 1940.

⁴²⁷ KEENEY, E. L.: *J. Allergy* 10: 590, 1939.

diseases, because it is believed to be attributable to a reactive production of epinephrine in the organism (Bartelheimer⁸²⁰)

In milder cases, epinephrine injection may be replaced by *ephedrine sulfate* injections (0.05 Gm or $\frac{3}{4}$ grain) or by the administration of any of the following sympathomimetic drugs: *ephedrine sulfate*, *propadrine hydrochloride*, *neosynephrin hydrochloride*, *benzedrine sulfate*. Friedman and Cohen⁸²¹ found *nethamine hydrochloride*, a new ephedrine like drug, to be rather effective in asthma and hay fever, and to be effective occasionally after *ephedrine* had failed. Hansel⁸²² employed it in combination with *theophylline isobutanolamine*. It can be administered intravenously, intramuscularly, or by rectal suppository when necessary. Since *ephedrine* is acted upon by the same enzyme (amine oxidase, found in blood and many tissues) as *epinephrine*, it tends to preserve the latter from being destroyed (Gaddum and Kwiatkowski⁸²³). The oral dose of *ephedrine sulfate* is 0.025 to 0.050 Gm ($\frac{3}{8}$ to $\frac{3}{4}$ grain) three or four times daily for adults, 0.010 to 0.015 Gm ($\frac{1}{6}$ to $\frac{1}{4}$ grain) for children between the ages of 6 months and 5 years, 0.005 Gm ($\frac{1}{12}$ grain) for infants under 6 months. Brown⁸²⁴ suggested the administration of an enteric coated tablet of *ephedrine* at bedtime in order to delay its action for three or four hours.

Ephedrine (1 to 2 per cent), *propadrine* (1 to 3 per cent), *neosynephrin* ($\frac{1}{4}$ to 1 per cent), and *privine* (*naphazoline*) (0.05 to 0.1 per cent) are also advantageously used for instillation into the nose, as is *benzedrine* by inhalation. Patients should be warned not to abuse these vasoconstrictors by overly frequent application.

Particularly useful are combinations of *ephedrine* with small doses of one of the barbiturates (*phenobarbital*), for counteracting the cerebral stimulation, and one of the xanthines, such as *aminophylline* or *theobromine*, which have a vasodilating and antispasmodic effect.

R	<i>Ephedrine sulfate</i>	Gm	0.025	gr	$\frac{3}{8}$
	<i>Phenobarbital</i>		0.015	gr	$\frac{1}{4}$
	<i>Aminophylline</i>		0.100	gr	$\frac{1}{55}$
D t	caps no xx				
Sig	1 capsule 3 times a day				

Aminophylline and other xanthines may also be administered by vein or by rectum and are particularly and often dramatically effective in terminating an attack of asthma.

Atropine acts on the condition of anaphylactic shock by paralyzing the parasympathetic nerve endings in the smooth musculature, and is thus able to stop or even prevent spasm of these muscles. The dose for attack is 1 mg ($\frac{1}{60}$ grain) subcutaneously. In less acute cases, $\frac{1}{4}$ to $\frac{1}{2}$ mg three times daily will suffice. *Atropine* is usually contraindicated in asthma, since it renders the bronchial secretions more viscid and hence more difficult to raise, thereby increasing the patient's distress. It is most useful in those cases of rhinopathy or hay fever with exceedingly profuse watery nasal discharge, which may be diminished by moderate doses by mouth, as well as in gastrointestinal allergy.

Ergotamine tartrate (*gynergen*) and *dihydroergotamine* (D H E-45) by mouth or subcutaneous injection are effective in the relief of migraine (see chap XXVI). The abdominal pain, nausea, and vomiting some times produced can be controlled by an injection of *atropine*.

Opiates, such as *morphine*, are mentioned only to be condemned. Although asthma may be relieved, their use is unsound because of their depressant effect on the respiration and on the cough reflex, causing retention of bronchial secretions and possibly suffocation, and they are therefore definitely dangerous. However, preliminary investigation indicates that *demerol*, a synthetic drug with anticholinergic, spasmolytic, and analgetic properties, may be less dangerous. It is employed by mouth or by injection in doses from 35 to 100 mg ($\frac{1}{2}$ to $1\frac{1}{2}$ grams) (Noth, Hecht, and Yonkman⁸²⁵), and may permit a reduction in the effective dose of *epinephrine* (Batterman and Himmelsbach⁸²⁶).

⁸²⁰ BARTELHEIMER H. Muenchen med Wchnschr 94 271 1944

⁸²¹ FRIEDMAN A J and COHEN A E. Northwest Med 43 138 1943

⁸²² HANSEL F K. Ann Allergy 1 199 1943

⁸²³ GADDUM J H and KWIATKOWSKI J. J Hyg 94 87 1938

⁸²⁴ BROWN E A. New England J Med 223 843 1940

⁸²⁵ NOTH P H, HECHT H H and YONKMAN F F. Ann Int Med 21 17 1943

⁸²⁶ BATTERMAN R C and HIMMELSBACH C K. J A M A 122 222 1943

Calcium decreases the excitability of the autonomic nervous system and the permeability of the capillaries. In our experience, however, this drug is effective only when administered in sufficiently large doses, and particularly intravenously in doses of 10 to 20 cc. of a 10 per cent solution. Except in cases of hypersensitiveness to bromide, we have found the following combination to be quite effective:

	Gm. or Cc
R Calcium chloride	
Sodium thiosulfate	\overline{aa} 10.0
Sodium bromide	3.0
Sterile distilled water	q s ad 100.0

Calcium chloride, while more effective than other calcium compounds, has the decided disadvantage that the slightest amount outside the vein, as may happen in patients with poor veins, will produce a painful necrosis. For this reason calcium gluconate is often preferable, and for intramuscular injection only the gluconate can be used.

Oral administration of calcium will be effective only in large doses given for a considerable period of time.

	Gm or Cc	
R Calcium chloride	24.0	} $\overline{5}$ vi
Distilled water	q.s. ad 360.0	
		} $\overline{13}$ xu

M. Sig.: 1 tablespoonful 5 times a day

R Calcium gluconate	0.5	} \overline{gr} viii \overline{ss}
Sig: 3 capsules or tablets 5 times a day		

Parathormone injections might also be mentioned here, because this mobilizes the body's own calcium. In human beings (Hajós) as well as in experimental animals (Docimo), these injections sometimes bring about a marked reduction in the manifestations of shock.

Potassium chloride, in a dosage of 0.3 Gm. (5 grains) three times a day, with a full glass of water, is said by Bloom to have an anti-allergic effect. Numerous attempts have been made to confirm the claim of clinical efficacy, but as a rule this drug has been found to be ineffective.

General anesthesia by ether, urethane, chloroform, etc., is said to prevent the onset of shock following reinjection of the antigen (Nikolaëff and Goldberg). While some successful animal experiments have been reported,

the anti-anaphylactic effect of narcosis in human beings is disputed. Moreover, this method involves the danger of unfortunate accidents. Thus, Quill reported a sudden respiratory death following administration of tetanus antitoxin to a patient under ether anesthesia.

No satisfactory explanation of the effect of anesthetics has been advanced. Besredka's original theory—that the shock is dependent upon the central nervous system and can thus be inhibited by reducing the excitability of the nervous centers—has been refuted by Doerr, who pointed out that the effect of narcosis is achieved in the periphery without the mediation of the brain.

General anesthesia (ether or cyclopropane by inhalation, ether or avertin by rectum) is sometimes indicated in status asthmaticus, but merely for its relaxant effect and to provide a period of rest for the patient.

Recent investigations seem to indicate that in the allergic individual various autonomic disturbances, both sympathetic and parasympathetic, frequently occur simultaneously. This might explain the beneficial effect often obtained with *Bellergal*, a preparation composed of a combination of bellafolin, gynergen, and phenobarbital (2 to 4 tablets daily). Mention should also be made of the favorable influence of *phenobarbital* (0.008 to 0.03 Gm or $\frac{1}{8}$ to $\frac{1}{2}$ grain, three times a day). The effects of this drug are attributable to its quieting influence on the basal ganglia of the brain.

Ethylene disulfonate (allergosil) has been advanced recently as a means for treating the allergic state, irrespective of the clinical picture, based on the concept of Evans, Bodman, and Maisin⁸⁷ that the allergic state is basically due to an abnormality of carbohydrate metabolism resulting from the absence in the body of certain catalysts of coenzymal activity. This drug was found in vitro to have the requisite properties. However, reports of its protective action against experimental anaphylactic shock could not be confirmed by Fisk, Small, and Foord.⁸⁸ Although

⁸⁷ EVANS, G., BODMAN, J., and MAISIN, J. H. *Med. Press & Circ.* 283: 5273, 1940.

⁸⁸ FISK, R. T., SMALL, W. S., and FOORD, A. G. *J. Allergy* 15: 14, 1944.

some favorable clinical reports have appeared (Smith,³³³ Wasson,³⁴⁰ and Bartlett³⁴¹), especially as regards pediatric allergies, they could not be confirmed by Archibald,³⁴² and Kurland and Buber³⁴³ found the preparation to have little if any therapeutic value in chronic bronchial asthma. Hence, caution must be enjoined³⁴³ until a more careful evaluation of its effects, based on thorough experimental and clinical investigation, is established.

The early optimistic results with the use of large doses of *ascorbic acid* (vitamin C) in the treatment of hay fever, asthma, food allergies, and other diseases of hypersensitiveness have not been confirmed by other investigators, including the authors. It may, however, be effective in the detoxification of the arsenicals.

Finally, *histamine* and *acetylcholine* therapy should be mentioned, since both are used, sometimes with satisfactory results, in certain cases of asthma (Dzsinich,³⁴⁴ Thiberge,³⁴⁵ Farmer³⁴⁶), urticaria (Ernstene and Banks,³⁴⁷ Alexander and Elliott,³⁴⁸ Porch³⁴⁹), cold hypersensitiveness (Bray,³⁵⁰ Roth and Horton³⁵¹), light hypersensitiveness (Capps and Young³⁵²), hypersensitiveness to insulin (Collens, Lerner, and Fialka,³⁵³ Roth and Rynearson³⁵⁴), and Meniere's syndrome (Horton³⁵⁴).

However, the present authors are of the opinion that the protection obtained with these substances is of the nature of a nonspecific pharmacologic tolerance rather than due to a nonspecific desensitization. In this connection, Alexander³⁵⁵ makes an interesting observation in his experience, histamine has no value

in the treatment of extrinsic allergy, in which the cause is a specific hypersensitiveness, but may be helpful in intrinsic allergy.

TECHNIC Except for the rapid intravenous method as used by Horton in the treatment of Ménière's syndrome (see p. 825) the average treatment schedule requires particular caution. The initial dose of 0.01 gamma or 0.00001 mg (0.1 cc of a dilution containing 0.0001 mg per cubic centimeter) is given intradermally. In the absence of untoward reactions subsequent doses are injected subcutaneously at forty-eight hour intervals. Successive doses of 0.2 cc 0.3 cc 0.5 cc and 0.8 cc of this dilution are given then the strength of the preparation is progressively increased until a dose of 0.1 mg (100 gammas) is reached. Final doses should not exceed 1 cc of the 0.1 mg per cubic centimeter concentration. A total of fifteen injections generally suffices.

Histamine is usually described in terms of histamine base. It is commercially available however as histamine acid phosphate and histamine dihydrochloride both preparations are standardized in terms of the U. S. P. anhydrous salt. 2.75 mg of the former and 1.5 mg of the latter being equivalent to 1 mg of histamine base. To convert to the quantity of base the diposphate may be multiplied by the factor 0.36 and the dihydrochloride by 0.66. Dosage may be calculated in terms of either the salt or histamine base but caution should be exercised lest these doses be confused. Recent preparations give both dosages e.g. ampule of histamine acid phosphate 2.75 mg in 1 cc (histamine 1:1000). Since the higher dilutions deteriorate rapidly, they should be prepared in comparatively small amounts at least once a week and kept refrigerated.

Intravenous histamine (1 mg diluted in 500 cc of isotonic sodium chloride solution) has recently been recommended for the treatment of migraine by Butler and Thomas.³⁵⁶

Histamine should be employed carefully, if at all, in aged or arteriosclerotic patients, and in asthmatic persons very small doses should be administered, as larger amounts may induce attacks. Following the injection, the face may flush rapidly, and with larger doses shivering and faintness may occur, accompanied by a fall in blood pressure and a rise in pulse rate. Such symptoms are ordinarily of short duration, lasting only fifteen to twenty minutes, if they are excessive, recourse may be had to epinephrine to control them. Shock, headache, and anginal pains in the chest may follow a large dose, although doses of several milligrams have been given by some observers to healthy subjects without apparent harm.

³⁵⁶ BUTLER C and THOMAS W. A. J. A. M. A. 128: 175, 1945.

³³³ SMITH N. M. Clin. Med. 51: 323, 1944.

³⁴⁰ WASSON V. P. Arch. Pediat. 60: 511, 1943.

³⁴¹ BARTLETT C. L. Arch. Pediat. 61: 311, 1944.

³⁴² ARCHIBALD H. C. Arch. Pediat. 62: 219, 1945.

³⁴³ KURLAND L. T. and BUBER H. M. Bull. School Med. Univ. Maryland 36: 46, 1945.

³⁴⁴ Current Comment. J. A. M. A. 120: 842, 1942.

³⁴⁵ DZSINICH A. Klin. Wchnschr. 14: 1612, 1935.

³⁴⁶ THIBERGE N. F. J. Allergy 6: 282, 1935.

³⁴⁷ FARMER L. J. Lab. & Clin. Med. 26: 802, 1941.

³⁴⁸ ERNSTENE A. C. and BANKS B. M. J. A. M. A. 100: 328, 1933.

³⁴⁹ ALEXANDER H. L. and ELLIOTT R. W. ibid. 114: 522, 1910.

³⁵⁰ PORCH L. D. J. Lab. & Clin. Med. 26: 499, 1940.

³⁵¹ BRAY G. W. J. Allergy 3: 367, 1932.

³⁵² CAPPS R. B. and YOUNG R. H. Proc. Am. Soc. Clin. Invest. 19: 778, 1940.

³⁵³ COLLENS W. S., LERNER G. and FIALKA S. M. Am. J. M. Sc. 188: 528, 1934.

³⁵⁴ ROTH G. M. and RYNEARSON E. H. Proc. Staff Meet. Mayo Clin. 14: 353, 1939.

³⁵⁵ HORTON B. T. Surg. Gynec. & Obst. 72: 417, 1941.

³⁵⁶ ALEXANDER H. L. J. Lab. & Clin. Med. 26: 110, 1940.

Histamine is contra-indicated during pregnancy and menstruation.

Since histamine is non-antigenic, *histamine-azoprotein complex* (Hapamine) was produced by Fell and his associates⁴⁴ by chemically combining histamine with despeciated horse serum globulin. While the histamine treatment per se is considered by the majority of authors as a form of pharmacologic rather than immunologic therapy, Sheldon and his associates⁵⁷ attempted to attain an active non-specific hyposensitization by the administration of histamine azoprotein. The theoretic goal was the production of antibodies to histamine that would neutralize any histamine liberated by any specific antigen-antibody union and would thus prevent the development of symptoms. Precipitins produced in animals (Fell⁴⁴) and in human patients (Cohen and Friedman⁴⁹) were at least partially specific for histamine. Animals were protected against anaphylaxis by immunization with this substance, and human beings appear to acquire a capacity for rapid histamine neutralization, which could also be demonstrated by means of skin tests with eserine (Cohen and Friedman⁵³). This method has been recommended for allergic conditions in which the allergen is not discoverable or cannot be completely avoided, or in which other therapy is ineffective.

TECHNIC. If an initial subcutaneous dose of 0.01 cc causes little or no reaction, subsequent doses every four or five days may be slowly increased (at first by 0.01 or 0.02 cc, later by 0.1 or 0.2 cc.) until 1 to 1.5 cc is being given. If intolerance is noted at any level, dosage should be reduced. Particular care should be employed in cases of contact dermatitis. When improvement occurs, the intervals between doses may be increased to one week or longer, but if symptoms recur, the entire course of therapy is begun again. Cohen⁵² has recommended a more intensive schedule, beginning with 0.1 cc., followed by 0.5 cc., and then by five 1 cc. doses at five day intervals. A similar series is given after a rest period of two months.

Sheldon⁵⁷ employed histamine-azo-despeciated horse serum globulin in the treatment of 76 allergic patients of various types. Cases of physical allergy seemed to be bene-

fited most, and promising results were also obtained in the dermatoses. Local reactions were frequent at the site of injection. No correlation was found between the dosage and the relief obtained. Warren and Findley⁵⁰ reported favorable results in the treatment of migraine, Derbes⁵¹ in asthma, and Cohen⁵² in urticaria and angioneurotic edema. However, increasing experience with this substance has revealed a considerable number of untoward reactions, even to very small or intracutaneous injections, and especially in patients sensitive to horse serum or dander (Dutton, Eyermann, Forman, Bowen, Edrington, Braden, Epstein—all in 1944 and 1945 International Correspondence Club of Allergy Letters—and Brown⁵³). These include not only extreme local reactions and alarming constitutional reactions, but also asthma, generalized urticaria, abdominal cramps, exfoliative dermatitis, and neuritis. We have observed a very severe anaphylactic shock with intense abdominal cramps appearing 5 hours after the fourth dose of this preparation. Further investigation of histamine-azoprotein, as regards both its therapeutic efficacy and its potential dangers, is necessary.

Another histamine derivative, B-(5-imidazolyl) ethyl carbamido protein, appears to afford some protection against anaphylaxis in animals (Rodney and Fell⁵⁴).

Histaminase, a histamine-inactivating enzyme, has been considered on pp. 104 ff. Clinical experience with it has been generally disappointing, except in some cases of physical allergy.

In the case of allergic patients who presented features of cholinergia, such as excessive sweating, salivation, indigestion of the hyperacidity type, intestinal spasticity, and dermatographism, Pearson⁵⁵ suggested injection of 0.5 mg. of an *acetylcholine* derivative (methyl) subcutaneously, increasing the dose daily by 0.5 mg. as long as tolerated. In general, 5 mg. is given weekly for two months.

⁵⁰ WARREN, E. W., and FINDLEY, T. M. *Clin North America* 29: 417, 1945.

⁵¹ DERBES, V. J. *Ibid* 29: 433, 1945.

⁵² COHEN, M. B., *Ohio State M. J.* 39: 1129, 1943.

⁵³ BROWN, E. A. *Ann Allergy* 3: 216, 1945.

⁵⁴ RODNEY, G., and FELL, N. *J Immunol* 47: 251, 1943.

⁵⁵ PEARSON, E. F. *Ann Int Med* 13: 2241, 1940.

⁵⁷ SHELDON, J. M., FELL, N., JOHNSTON, J. W., and HOWES, H. A.: *J Allergy* 13: 18, 1941.

⁵³ COHEN, M. B., and FRIEDMAN, H. J. *Ibid* 15: 245, 1944.

⁵⁴ COHEN, M. B. *Ibid* 15: 274, 1944.

If a general reaction occurs, it can be controlled by applying a tourniquet above the site of injection. Pearson holds that by daily cholinergic stimulation with mechohyl one may stimulate more efficient cholinesterase action. This is the enzyme that normally causes immediate destruction of acetylcholine in the tissues. Pearson reported good results in cases of asthma, urticaria, and angioneurotic edema. Logue and Laws,⁴³ however, were unable to confirm this effect in cases of asthma.

Benadryl, a synthetic antihistamine preparation, offers great promise in the treatment of a number of allergic diseases. Intravenous administration (60 mg in 100 cc of saline solution) has been found to provide rapid relief of acute symptoms of hay fever, rhinopathy, urticaria, angioneurotic edema, vascular headache, and the early stages of Meniere's syndrome. Sustained relief requires continued therapy by intramuscular injections (20 mg), which are moderately painful, or orally (50 to 100 mg two to five times daily). The larger doses, particularly by mouth, rather often produce side effects of drowsiness, dizziness, weakness, dilated pupils, dry mouth and nervousness though rarely of sufficient severity to necessitate discontinuance of therapy. Rarely, acute nausea and vomiting occur. The optimum daily dose for children is 2 mg per pound of body weight divided into two to four doses. The drug appears to be particularly efficacious in urticaria and physical allergies. (See also pp 105, 755.)

4 IRRADIATION TREATMENT

Rays (roentgen, grenz, ultraviolet) may exert their anti-allergic influence in three ways (1) by metaspecific hyposensitization, (2) by nonspecific reduction of the sensitivity (3) by stimulating the reticulo endothelial system to increased antibody production.

An example of metaspecific hyposensitization is presented by any irradiation treatment that is sufficiently strong to result in slight damage to the tissue. Thus, the favorable therapeutic effect of X rays for example, may be compared with that of foreign protein therapy. Because of the protein disintegration as chemically demonstrated by Urbach and Schnitzler,⁴⁴ break

down products are formed that act as met antigens in the allergic organism. Both Hajos and Capelli have shown the anti-allergic influence of roentgen rays in animal experiments. Furthermore the studies of Simanko, Abramovitch and Rabuchin and others should be mentioned here. Their various results however are not quite comparable since the effect of the rays depends upon a number of conditions that varied in each of the studies (e.g. type of tube, quality of rays—hard or soft—filtration, type of animal, skin site, concentration of antigen, etc.).

Miescher made the first systematic investigations of nonspecific reduction of sensitivity by means of roentgen irradiation in dermatitis. In approximately half of his cases, he observed a temporary reduction of reactivity about ten to twenty days after the roentgen irradiation, that is, at the peak of the reaction. He attributed this effect to a nonspecific inhibition of the process of inflammation. However, Miescher was not able permanently to change the hypersensitivity of the skin. Schreus and Willms on the other hand report that by using unfiltered rays they produced in 9 of 14 dermatitis cases a state of reduced reactivity lasting for many weeks. They attribute the recurrence of the hypersensitivity to the fact that the rest of the skin was not similarly rendered insensitive and suggest mild irradiation of the entire skin surface in allergic skin diseases. A similar if not identical view had previously been advanced by Bucky, who recommended general irradiation with grenz rays.

Finally, the third possibility—namely, the effect of the rays with regard to stimulation of the reticulo endothelial system to increased antibody production—must be briefly considered. We prefer to discuss this theory as a working hypothesis here, rather than in connection with metaspecific hyposensitization. In the latter, the titer of specific antibodies is increased by metaspecific agents, whereas in the mechanism under consideration, the reticulo endothelial system is stimulated for the purpose of greater antibody production.

Numerous authors have demonstrated in various ways that general irradiation with small roentgen doses (and also with radium and strong sunlight) increases the activity of the

reticulo-endothelial system. Indeed, Urbach and Wiedmann⁵⁵⁸ were able to show that irradiation affects chiefly the reticulo-endothelial system of the skin. When animals were injected intracutaneously with extracts of irradiated and nonirradiated skin, then tumor material introduced into these sites twenty-four hours later, a response was observed consisting of a great swelling in the sites of the injection of nonirradiated skin extract, while the sites that had been injected with irradiated skin extract presented either no cancer formation whatever or nothing more than an evanescent epithelial thickening. The results were excellent when unfiltered roentgen, radium, or grenz irradiation was given, not nearly so good with moderate filtration, and quite poor when heavy filters were used. These findings coincide with the microscopic studies, for a definite increase in the reticulo-endothelial cells (histocytes) of the skin is seen only after mild, superficial irradiation. The results of these investigations (nonspecific increase in antibodies as the result of functional stimulation of the reticulo endothelial system of the skin) may explain at least some of the beneficial effects of roentgen irradiation in allergic skin diseases.

A discussion of the favorable effects of roentgen irradiation on asthma and allergic rhinopathy will be found on pages 643 and 507.

5. HABITUATION OR TOLERANCE

"Habituation" or "tolerance" designates a decreased reactivity to a given chemical substance or physical agent that previously produced a pathergic reaction. Thus, there is habituation to certain drugs—commonly called "drug fastness"—and also to narcotics, alcohol, and tobacco, commonly known as tolerance. One speaks of refractoriness, or reactive exhaustion, when the skin no longer reacts to a given substance (e.g., histamine) that previously had repeatedly evoked an inflammatory reaction.

The methods of habituation have been employed chiefly in the physical hypersensitivities (due to pressure, cold, heat, light). Duke^{559 467} was probably the first to resort to systematic application of cold water in the management of urticaria due to cold; to irradi-

ation with a 1,500-watt nitrogen lamp in treatment of urticaria due to heat, to increasing exposure to the type of light that was not tolerated, and to frequent rubbing of the skin with a hard brush in cases of mechanical urticaria (Fig 77). Lehner and Rajka have reported not only local but also general "desensitization" in cases of urticaria factitia. Vallery-Radot and Blamoutier were able to cure cold urticaria with systematic cold hand baths. The senior author cured a severe



FIG 77 EXHAUSTION TREATMENT OF DERMOGRAPHISM

Skin area in outlined square was rubbed with increasing force twice a day for ten days. Distinctly less marked response in this region contrasts with that below, produced in area not previously treated.

cold urticaria in a surgeon by means of systematic cold showers. P. S. Meyer, Volk, and Sellei and Liebner, as well as others, succeeded in eliminating or at least definitely decreasing light hypersensitiveness in cases of hydroa aestivale by systematic irradiation with gradually increasing doses of ultra-violet rays during the winter months.

The list of therapeutic measures designed to "accustom" the patient might well include the use of breathing exercises in asthma and rhinopathy, since the mucuous membranes of the

nose and bronchi thus become accustomed to irritation from without

Finally, we should also mention here the procedures designed to harden the skin. J. Jadassohn, and also Eller and Schwartz⁶⁶⁵ have pointed out that continuous contact with irritants tends to harden the skin, while in intermittent contact fails to do so. Peck et al.⁶⁶⁹ found that 'hardening' occurs frequently in workers with industrial contact dermatitis, but not in all individuals and may be overcome by exposure to a greater concentration of the sensitizing chemical than that to which tolerance has been established. It may be permanent, but in most instances it disappears if the exposure to the allergenic agent is discontinued for any length of time.

Torok is of the opinion that the changes in the reactivity of the skin, which increases after the first three or four mechanical thermal, or electric stimulations and decreases on subsequent exposure, is attributable to the action of tissue substances formed during the course of the reaction in the skin. According to this author, there are two groups of such tissue substances, one of which—corresponding to the H substance of T. Lewis—increases the reactivity, while the other—provisionally called the R substance by Torok—decreases it. The habituation of the skin to the influence of external agents is probably the result of the increased production of the R substance. These substances are not to be confused with the skin sensitizing or blocking antibodies of Cooke and of Lehner and Rajka (see p. 143).

6 PSYCHOTHERAPY

Every physician who has had much to do with allergic individuals knows what an important part is played by psychosomatic influences in the production of allergic conditions, he readily understands, therefore, that these influences must be accorded very special consideration in connection with the treatment of these patients. To avoid repetition, the reader is referred to the pertinent experiments and examples given on page 74. Consequently, every allergist must be capable of giving

advice and treatment along psychic lines. In some isolated and especially severe cases it may be advisable to refer the patient to a psychiatrist with training in allergy.

However in the vast majority of allergic patients the conscientious physician with an elemental knowledge of psychic relationships and with a sympathetic and reassuring attitude is fully capable of handling the situation. In fact, his so doing will avoid a certain amount of psychic trauma inherent in a formal neuropsychiatric consultation many patients being totally unaware of any connection between their emotional life and their symptoms, and consequently resistant, at least at first, to any suggestion of this sort. However, in time, nearly every patient in whom psychogenic factors are of any considerable importance can be led to an acceptance of this idea.

It is important, if not essential for the allergist to determine whether psychogenic components constitute the direct and sole cause of the allergic complaint, as only rarely happens whether they act as predisposing factors or as a trigger mechanism or whether they are merely the secondary result of a chronic, often incapacitating disease. For it must be realized, with respect to the last mentioned possibility that allergic conditions frequently are the cause of considerable economic disability, social dislocation and interference with normal domestic and family relationships. The extent to which the patient employs his complaints for the purpose of gaining conscious or subconscious ends, as in pampered child or housewife or to achieve family domination, or to excuse failure to meet a competitive situation should receive consideration. In such instances, alteration of the family relationship so as to remove the "psychic gain" may produce gratifying results.

Appropriate psychotherapy requires no formalized approach. Allowing and indeed, subtly encouraging the patient to discuss freely and without embarrassment not only his complaints, but also apparently unrelated sources of unhappiness, fears, and feelings of inadequacy and insecurity may be all that is necessary. This may require several interviews. In others, persuasive comments tending to give the patient insight into certain less

⁶⁶⁸ ELLER J. J. and SCHWARTZ L. *New York State J. Med.* 35: 951, 1935.

⁶⁶⁹ PECK S. M., GANT J. Q. JR. and SCHWARTZ L. *Indust. Med.* 14: 214, 1945.

apparent interrelationships, to overcome psychologic maladjustments, and to lead him to arrive at a feasible solution of his problems are necessary. Sexual conflicts should be dealt with by appropriate means. In many cases, a carefully phrased chat with other members of the family or with close associates, sometimes without the patient's knowledge, is of value, both in eliciting information and in correcting frictions arising in the home or at work. When necessary, removal of the patient from unpleasant or intolerable surroundings, often under the guise of a "trip" or a change in climate, is followed quite frequently by an

amazing improvement. Finally, repeated reassurance that his disease is not incurable, at least in the sense of obtaining symptomatic relief, that life need not be unsatisfactory and burdensome for the rest of his days, and that he may look forward to a useful, happy future, constitutes an invaluable feature of psychotherapy.

It must be apparent from the foregoing that perseverance and confidence, on the part of both the physician and the patient, are two definite prerequisites for the successful treatment of allergic patients.

ETIOLOGIC AGENTS OF ALLERGIC DISEASES

THE second part of this book will be devoted to discussion of the substances eliciting allergic responses. In Part One it was shown that the pathogenic mechanism of an allergic disease is the result of the combined effect of predisposing factors and eliciting agents. The various predisposing influences have been discussed in detail; the provocative agents will be considered here.

Up to the present time, the allergic agents of external origin have for obvious reasons received the greatest share of attention and study. Relatively little is known about the secondary exogenous and the endogenous allergens, the salient facts about them have been covered in chapter IX.

At present, it is impossible to subdivide the primary exogenous allergens according to any single principle. For practical reasons, however, we have resorted to the following more or less arbitrary categories: inhalants, ingestants, injectants, contactants, physical agents, insectants, and parasitic agents. The difficulties involved in arriving at one fundamental principle of classification make a certain amount of overlapping unavoidable. We have tried, however, to obviate this as far as possible by proper cross references.

It will be apparent to the reader that many substances are capable of exerting an allergenic influence by way of more than one route of entry. To cite just a few examples: Penicillin may produce manifestations of hypersensitiveness after injection, ingestion, or contact with the skin. The same food which causes urticaria, asthma, or rhinopathy when eaten by some individuals, may be responsible for dermatitis of the hands, circumoral region,

or eyelids when allowed to contact these areas, in the same or other patients. And, indeed, the odor of foods may affect still others. House dust and pollens, which are of such notable importance as inhalants, can also act as contactants. Numerous similar instances will be found in the ensuing pages.

Aside from any other reason, considerations of space alone would make it impossible to present anything like a complete list of all the substances and combinations of substances that have, at one time or another, been reported as evoking hypersensitivities. The important causative substances vary greatly from country to country, and even from locality to locality, depending to a great extent on the local flora, on the species of animals most frequently encountered, on the use of certain apparel, comestibles, chemicals, and cosmetics, on the dietary customs, and so on. Nevertheless, we shall attempt to point out the most important allergens, and to discuss briefly their distribution in nature, in food, in fabrics, and in other ways in the environment.

A knowledge of these facts is essential, both in properly evaluating the patient's exposure as a first step in establishing the etiologic diagnosis, and in planning an effective therapeutic regimen. For many allergenic substances occur in unrecognized or "hidden" form, so that their detection requires some understanding of the components of prepared foods, the composition of cosmetics and fabrics, and the ingredients of proprietary drugs and dentifrices. In fact, it is not too much to say that the allergist must be cognizant of the totality of the environment of his patients.

CHAPTER XIII

INHALANTS

IT HAS become increasingly apparent during the past few years that the majority of cases of asthma and allergic rhinopathy that are of exogenous allergic origin are due to inhalation of epidermal substances, house dust, pollen, mold, smuts, rusts, or volatile oils. In addition, occasional cases of urticaria, angioneurotic edema, neurodermatitis, and migraine may also be brought on in this manner.

A. DUST

Dust is certainly the most important of the inhalant allergens, especially in relation to asthma. We do not refer to the nonspecific mechanical irritation caused by street or field dust, for example, but shall consider only those cases that react specifically to dust with allergic manifestations.

In the following discussion, we shall have to differentiate between house dust and certain occupational dusts. The latter are commonly the cause of rhinopathy and asthma in millers, threshers, bakers, confectioners, carpenters, cabinet, cigar, brush, rope, harness and mattress makers, pharmacists and chemists, jewelers, laboratory workers, upholsterers, wool sorters, furriers, cotton spinners and weavers, and grocers. The chief difference between the occupational dusts and house dust is that the allergenic ingredients of the former are, by and large, known, and are usually of protein nature. House dust, on the other hand, is a material of highly complex nature, as will be shown later. Cases of hypersensitiveness to dust of inorganic nature are quite rare. However, there is Hofbauer's report⁷⁷ on a patient with asthma who had attacks only on passing through a certain district. Geologic investigations revealed the presence of a special kind of stone known as flysch. When the patient's bronchial mucosa was sprayed with a suspension of this material, typical asthmatic symptoms appeared. Moreover, the writers have observed a few cases of asthma in infants evidently caused by dusting powders, though whether on a specific allergic basis or as a

result of mechanical irritation has not been determined. The attacks occurred while the child was being powdered.

Common street dust is composed of both inorganic and organic constituents. The inorganic constituents consist of fragments of the various paving materials and of earth, while the organic part is composed, according to the season, of pollen, mold spores, fragments of leaves, insects, plants, bark, chaff, and constantly of animal hair, bits of feathers, clothing, shoes, etc. These specific dust allergens will receive more detailed consideration in appropriate sections elsewhere in this book.

We are here exclusively concerned with the question of hypersensitiveness to house dust. Kern⁷⁸ and Cooke⁷⁹ first called attention to the special significance of house dust in the causation of asthma; their findings have since been confirmed by numerous authorities. Among asthma cases tested by Cooke and McLaughlin, 33 per cent gave positive reactions to house dust, while Clarke and Burt report 73 per cent, and Pratt's figure is as high as 79 per cent. It is important to note that asthma and rhinopathy are not the only conditions that may be caused by the inhalation of dust. Vaughan⁸¹ has demonstrated that angioneurotic edema can also be brought on in this manner. The senior author has seen a case of urticaria due to this mechanism.

It must be emphasized, however, that a positive cutaneous reaction to house dust in a given case does not, in itself, constitute conclusive proof of the etiologic significance of the dust; the appropriate elimination and exposure tests must be performed before any definite conclusion may be drawn.

Despite all the experimental investigations that have been undertaken along this line, we do not as yet know just what the actual excitant in house dust is. Depending on its origin, house dust may contain any or all of the following constituents: substances from animal and vegetable sources, such as feathers

⁷⁷ KERN R A. *M Clin North America* 5: 751, 1921.

⁷⁸ COOKE R A. *J Immunol* 7: 147, 1922.

from pillows, horse and rabbit hair, dander from household pets and the like, human dander, glue, cotton, wool, silk, and flax fibers from clothing, bedding, upholstery, rugs, and drapery, as well as kapok, felt, jute, pollens, parts of plants and of flowers, orris root, pyrethrum and other insecticides, tobacco, bacteria, mold, fungi, scales of moths and, in rural districts, also of butterflies. Numerous attempts have been made to trace the antigenicity of house dust to one or more of its ingredients. Albert, Bowman, and Walzer⁵⁷² concluded from clinical and passive transfer studies that, when dust antibodies are found, they are present also to other dust producing inhalants, such as wool, feathers, danders, cottonseed, flaxseed, silk, or pyrethrum. Davidson⁵⁷³ found that patients who were skin-sensitive to house dust showed a high incidence of positive reactions to horse dander, cow hair, and cat hair, and less often to feathers and wool. These findings and opinions are not shared by the vast majority of allergists. It is generally agreed that, while the items listed above and innumerable other things combine to form house dust, its extract contains a specific antigenic principle that is not identical with any of its ingredients (Cooke⁵⁷¹). This was confirmed by the Schultz-Dale experiments of Hampton and Stull.⁵⁷⁴ While animals sensitized to house dust also gave reactions to other antigens that might be present in the home, such as animals' danders and feathers, desensitization with any of the latter did not desensitize against house dust antigen. Moreover, dust from homes where the other common inhalant allergens were absent gave as good antigenic responses as any other samples.

Investigations carried out by Cohen et al⁵¹⁵ suggest the possibility of an allergenic factor being formed by the deterioration of the material composing the dust. It was found that when fresh cotton lintens were kept for some months—after having been sealed in an airtight jar and autoclaved for one hour at a temperature (120 C.) believed to be high enough to kill all molds and bacteria—they

developed an allergenic property identical with that possessed by house dust. The authors concluded, therefore, that the reacting substance in house dust is some deteriorated product of cotton lintens developed during the aging process. Guinea pigs could be sensitized and shocked with this lintens extract.⁵⁷⁶ There is evidence that other organic substances, such as feathers or kapok, may produce a similar allergen on aging.

On the other hand, it must be stressed that it has not as yet been possible to demonstrate the existence of a single characteristic antigenic entity in house dust (Coulson and Stevens⁵⁷⁷). Adelsberger claims that the active principle in house dust is heat-resistant and insoluble in the usual solvents, with the exception of water. It is reasonable to conclude that although little is known about its nature, "house dust" is a specific antigen, unrelated to other recognized inhalants.

Aside from the specific antigen, house dust also contains a toxic principle that may very well explain the anaphylactoid manifestations occurring after injections of large doses of extract (Coulson and Stevens; Friedman). In order to eliminate the toxic factor and irritant constituents producing non-specific whealing reactions, Efron and his associates^{573, 579, 580} prepared a purified house dust extract* by means of two successive fractional precipitations with dioxane, two successive precipitations from concentrated ammonium sulfate solution, and dialysis, obtaining a stable substance of protein nature, but also containing carbohydrate. Solutions of this preparation up to and including 0.002 per cent were not irritating, and it was shown to have high diagnostic specificity and therapeutic efficacy. Investigations carried out by Besser in Dr. Urbach's department, and by the junior author, confirmed the dependability of the purified house dust extract.

Sutherland⁵⁸¹ described a method for extracting house dust with N/100 ammonia

⁵⁷² ALBERT, M. M., BOWMAN, E. L., and WALZER, M. J. *Allergy* 9: 392, 1938.

⁵⁷³ DAVIDSON, M. T.: *ibid.* 14: 244, 1943.

⁵⁷⁴ HAMPTON, S. F., and STULL, A.: *ibid.* 11: 109, 1940.

⁵⁷⁵ COHEN, M. B., NELSON, T., and REINARTZ, B. H.: *ibid.* 6: 517, 1935.

* Available from Endo Products, Inc., Richmond Hill, N. Y.

⁵⁷⁶ COHEN, M. B., COHEN, S., and HAWVER, K.: *ibid.* 10: 561, 1939.

⁵⁷⁷ COULSON, E. J., and STEVENS, H.: *ibid.* 11: 537, 1940.

⁵⁷⁸ EFRON, B. G., BOATNER, C. H., and PARST, M. R.: *J. Invest. Dermat.* 4: 99, 1941.

⁵⁷⁹ BOATNER, C. H., EFRON, B. G., and DUFMAN, R. L.: *J. Allergy* 12: 176, 1941.

⁵⁸⁰ BOATNER, C. H., and EFRON, B. G.: *J. Invest. Dermat.* 5: 7, 1942.

⁵⁸¹ SUTHERLAND, C.: *Brit. M. J.* 2: 250, 1942.

and precipitation with sodium benzoate which yields a product that is largely carbohydrate of marked reactive capacity and therapeutic activity

It should not be overlooked, however, that in a certain number of cases the causal allergen is not the dust itself, but one of its components (e.g., pollen, molds, mites). Thus, the writers found dust consisting of the deteriorated bodies of mites to be the cause of rhinopathy in as librarian who was in constant contact with old folios and parchment books. It should be emphasized that patients reacting to house dust should also be tested with other common inhalants, and on the basis of the history, consideration of environmental exposure, and the relative size of skin tests, a decision reached as to the exact nature of the patient's allergens, thereby enabling proper environmental control and specific treatment.

The question frequently arises whether, for diagnosis or treatment, dust from the patient's own home or a mixture of dusts from others' homes (stock dust) should be used. While it is true that the patient is much more exposed to the former, and that there is the possibility of its containing some individual factor, it is the experience of many authors that a stock dust sometimes elicits stronger reactions. Accordingly, tests should be carried out with both.

TECHNIC The dust is collected from the patient's environment by putting a new bag on the vacuum cleaner used in the patient's home and then thoroughly sweeping all the rugs, carpets, draperies up, holstered furniture, mattresses, pillows, etc., in the house. In order to obtain a sufficient quantity of each kind of dust it is advisable to beat and shake each article. Of course this work is not to be done by the patient (detailed instructions will be found on p. 288). Dust so prepared in the case of an individual patient is conveniently but erroneously called "autogenous" dust. It is extracted for two days with frequent shaking in about ten times its weight of Coca's solution (consisting of 9 Gm. sodium bicarbonate, 500 cc. of physiologic saline solution and 450 cc. of distilled water, 50 cc. of a 1:10,000 aqueous solution of merthiolate is added to the finished extract as a preservative). After filtration through several thicknesses of gauze and once through filter paper it is passed with aseptic technic through a Seitz filter and placed in sterile rubber stoppered vaccine vials. A sample is cultured for sterility by aerobic and anaerobic methods, if any growth is obtained it must be re-filtered and re-tested. Nitrogen content may be determined by the micro-Kjeldahl method as a rough indication of potency,

although standardization according to nitrogen content is not recommended. By adding 1 cc. of this extract to 9 cc. of the diluting solution a 1:10 dilution is prepared by similar successive steps 1:100 and 1:1,000 dilutions are obtained.

If definite, specific (not irritative) reactions are obtained on testing with stock or "autogenous" dust extracts, if other inhalant constituents of dust are not responsible, if clinical confirmation exists (condition worse indoors and in winter, aggravated by dusting and bed making), and if the dust precautions given elsewhere are therapeutically inadequate, intracutaneous hyposensitization is cautiously administered.

TECHNIC It is best to start with 0.05 or 0.1 cc. of a 1:1,000 or sometimes of a 1:100 dilution and to increase the dose twice each week by 0.05 cc. provided severe local or focal reactions do not appear. After 0.3 cc. is reached the next dose is 0.05 cc. of a concentration ten times stronger and so on to the limit of the patient's tolerance or to a maximum dose of 0.3 cc. of the concentrated extract. After a while one weekly injection will suffice later in the course of the treatment the regimen should be one injection every two weeks continuing at that frequency until clinical insensitivity is attained.

An oral method for hyposensitization to dust was suggested by Barksdale⁷⁹² and Blackmar.⁷⁹³ The writers can confirm the value of this approach with their own results, employing the following slightly modified technic:

TECHNIC The dust is collected as indicated above including a fair amount of mattress stuffing. A quantity of this is extracted with about four times its weight of glycerinated saline (equal parts of physiologic saline solution and glycerine) for seventy-two hours. After filtration this is passed through a Berkefeld or Seitz filter tested for sterility, and 1:10,000 merthiolate is added as a preservative. This is considered a concentrated extract. From this a 1:100 dilution is prepared and the patient is directed to take 1 drop in water three times daily a half hour before meals. The quantity is doubled each day until a dose of 64 drops is reached. If no untoward reactions intervene the same procedure is followed with a 1:10 dilution. Finally the concentrated extract may be used with very cautious increase of the dose drop by drop until the amount of a teaspoonful is reached. However in some patients a quantity greater than 3 or 4 drops may cause focal or gastro-intestinal reactions. When satisfactory clinical results have been achieved the dose is kept constant for a few weeks after which the interval between doses may be gradually lengthened.

⁷⁹² BLACKMAR, F. B. *Tr. Am. Laryng. Rhin. & Otol. Soc.* 1940, p. 356.

B. AGENTS OF ANIMAL ORIGIN

1. EPIDERMAL SUBSTANCES

The group of epidermal allergens includes animal and human dander, hair, hides, sheep's wool, and feathers.

The epidermis of animals (dander) is quite commonly the cause of asthma and of allergic rhinopathy, less often of dermatitis, urticaria and migraine. It is noteworthy that such patients are seldom aware of the cause of their trouble. But it is relatively easy in cases involving epidermal antigens—easier than in the case of most other allergenic agents—to demonstrate the connection and frequently to effect prompt relief. In many cases the hypersensitiveness is strictly specific—that is to say, an individual who is hypersensitive to dogs can tolerate the presence of cats, and a case of hypersensitiveness to goose feathers will not be affected by a pillow stuffed with chicken feathers. But there is also such a thing as allergy to an entire group of substances: e.g., hypersensitiveness to all types of feathers, or to hairs of any member of the cat family (lions, tigers, panthers, leopards, lynx).

Horse dander is a common cause of asthma and rhinopathy in farmers, cavalymen, equestrians, jockeys, stablemen, and veterinarians. But these individuals are by no means the only ones who are prone to this hypersensitiveness. For example, Feinberg⁵⁴ reports the case of a young asthma patient who suffered an attack every time his mother came home from a horseback ride. Highly hypersensitive individuals can be affected by mere traces of horse dander in the air emanating from a near-by stable, for example, or from manure used on nearby lawns or gardens.

An individual who is hypersensitive to horse dander is not necessarily allergic to horse serum. Forster⁵⁵ and Ratner⁵⁶ have demonstrated that horse dander and horse serum contain the same antigen, but there is relatively less of the antigen in the dander than in the serum. Moreover, the dander contains another antigen that is not present in the serum. "Horse asthmatics" who are hypersensitive to both allergens will therefore react to horse serum as well as to dander; but those

who are allergic only to dander will tolerate the serum. This important fact led Tuft⁵⁵ to stress the necessity of performing conjunctival and skin tests to ascertain whether or not an individual who is clinically allergic to horse dander is actually hypersensitive to horse serum. Hartmann⁵⁶ has investigated this question thoroughly, and concluded from history, skin tests with extracts of cutaneous scales, urine, and sweat of horses, and horse serum, as well as clinical observation, that there is no relationship between sensitivity to horse emanations and that to horse serum, nor to the ingestion of horse meat. Similarly, Duke reported the case of a man who could not tolerate the proximity of a horse, but who gave no reaction whatsoever to a subcutaneous injection of horse serum.

Hypersensitiveness to *horsehair* is encountered not only in the occupational groups mentioned above, but also among upholsterers, harness makers, and all persons whose work brings them into frequent contact with uncleaned horsehair. Furthermore, there are patients who are regularly exposed to this allergen by reason of mattresses, cushions, pillows, sofas, chairs, and automobile seats stuffed with horsehair. The padding used under rugs is a particularly potent source of the allergen because of the short and relatively unprocessed hair (horse and cow) incorporated, and of the frequent agitation (Feinberg⁵⁴). Felt hats are also to be borne in mind in this connection, for felt is sometimes made of horsehair alone or from a mixture of this with other hair. Coats made of pony skin and children's toys covered with horsehide must also be mentioned here. Because of the careful cleansing and chemical treatment, the horsehair used for the padding of coats and for similar purposes is less likely to cause trouble.

Second in frequency are the epidermal emanations of *dogs* and *cats*. These cases sometimes present an extraordinary degree of hypersensitiveness. The writers, for example, have observed asthma or coryza to occur after the neighbor's dog or cat has merely lingered for a few moments in the patient's garden. Direct skin tests and cross-neutralization tests

⁵⁴ FORSTER, G. F. J. *Exper. Med.* 47: 903, 1924

⁵⁵ RATNER, B., and GREEEL, H. L. *Arch. Path.* 8: 635, 1929

⁵⁶ TUFT, L. J. *Allergy* 6: 29, 1934

⁵⁷ HARTMANN, W. *Zschr. f. Immunopathologie u. exper. Therap.* 99: 237, 1941

performed by Hooker⁸⁸⁷ indicate that danders from various species of dogs may possess qualitative antigenic differences. Clinical observations on some dog sensitive patients would tend to conform with this. As yet no adequately multivalent extract of dog dander has been devised. While allergy to dogs is almost exclusively dependent upon the presence of the living animal, manifestations of hypersensitivity to cats can also be elicited by fur coats, carriage robes, fur caps, gloves, slippers, etc. made of cat fur. Cat hair is often found on toy animals as well. It must be remembered, furthermore, that individuals who are hypersensitive to cat hair are very frequently unable to tolerate furs of other animals of the cat family (leopard, caracul, lynx, panther, wildcat, jaguar, tiger, lion).

Hypersensitivity to rabbit dander is of very special significance. This condition is not uncommonly encountered in people who raise rabbits as well as in physicians and laboratory workers who frequently experiment on these animals. Furthermore, rabbit hair is very widely used industrially, chiefly as stuffing in cheap pillows, mattresses, and upholstery. According to Ratner,⁸⁸⁸ and Larsen and Bell,⁸⁸⁹ rabbit hair in bedding, for example, is frequently an eliciting factor, particularly in juvenile asthma. Furthermore, rabbit pelts are extensively used in imitations of other furs. The physician must not permit himself to be misled by the high sounding name with which the patient may endow her furs for many a so called white, black, or red fox, many an alleged lynx, ermine, sable, nutria, chinchilla, muskrat or Hudson Bay or electric seal may in fact be nothing more or less than skilfully dyed and trimmed rabbit fur. Rabbit hair is also used in the manufacture of cheap felt hats, and of the felt used for insulation, as well as for all sorts of padding. The hair of the Angora rabbit makes an excellent yarn for the manufacture of underwear, sweaters, scarves, gloves, and other types of apparel.

Hypersensitivity to cow hair occasionally occurs in the rural population, as well as among butchers. It must be remembered,

furthermore, that cow hair is employed in the manufacture of cheap mattresses, bolsters, upholstery, horse blankets, carpets, rugs, carpet padding, felt and socks as well as of toy animals.

Hypersensitivity to goat hair was encountered quite frequently by Peshkin⁸⁹⁰ in asthmatic children in New York. This may be explained by the fact that Italians in New York quite commonly use goat hair in bedding. But goat hair is also employed extensively in industry. The hide, with the hair attached, is used as fur or made into rugs. Mohair—the hair of the Angora goat—is widely used for plushes (for automobile and railroad car seats), velvets, covering and trimming of upholstered furniture and for portieres, as well as for carriage robes and muffs. Mohair is also made into yarn and used alone, or mixed with wool or silk, for dress goods, coats, suits, socks, and gloves. The hair of the Cashmere goat is used principally for the manufacture of shawls.

Camel hair can also be the cause of allergy. Often mixed with wool, camel hair is used to manufacture camel's-hair cloth, for blankets, overcoats, underwear, and in felts and hats, and also rugs and carpets.

Hog hair or bristles have been identified as the causal allergen in occasional instances. These hairs are used in shaving brushes and toothbrushes and also as a cheap filling material in upholstered furniture and mattresses.

Both the hair and the dander of guinea pigs, mice, rats, and monkeys have occasionally been shown to be the cause of asthma and of coryza in laboratory workers and others in contact with these substances.

While the hair and hide of any animal can, in principle, elicit allergic manifestations as a result of inhalation, this is particularly true of furs. Thus in fur workers and dealers and less often in individuals wearing the furs, asthma and rhinopathy of this origin are encountered. It is worth noting, however, that there is a much lower incidence of allergy to genuine, high priced furs—probably because of the greater care taken in cleaning and treatment in general—than to the cheap rabbit and cat furs. As for the hypersensitivity to all the types of hair mentioned, it need only be

⁸⁸⁷ HOOKER, S. B. *Ann. Allergy* 2: 251, 1944.

⁸⁸⁸ RATNER, B. *Am. J. Dis. Child.* 24: 346, 1922.

⁸⁸⁹ LARSEN, N. P. and BELL, S. D. *ibid.* 24: 41, 1922.

⁸⁹⁰ PESHKIN, M. M. *ibid.* 31: 63, 1926.

said that, in view of the countless millions of fur coats, and other articles of clothing worn, the incidence of allergy to these potential agents is extremely low. This is probably due to the fact that in the course of the manufacturing processes the animal hairs are subjected to considerable chemical and physical changes.

The same is true of *sheep's wool*. Although most extensively used in suits, dresses, sweaters, coats, shirts, shawls, and capes, as well as in blankets, robes, carpets, and rugs, wool is not especially important as a causative agent in asthma and rhinopathy, except in those instances in which individuals come into contact with wool in its natural state. Thus, Moll⁵⁹¹ reports that in certain districts of England, in which the woolen industry is located, wool allergy is the cause of about 18 per cent of asthma cases. Prausnitz⁵² determined that the incidence of asthma among the wool combers working in the English spinning mills was 20 per cent. He also found wool to be a common cause of asthma among those engaged in sorting or knitting wool. It is important to note that these findings could be established only by means of bronchial tests; skin tests consistently failed to reveal hypersensitiveness to wool. Sufficient study has not yet been devoted to the question as to whether inhalation or direct contact with wool is the cause of the exacerbations in cases of dermatitis in infants, who so often manifest hypersensitiveness to wool.

A place of special importance among the inhalant allergens is occupied by *feathers*. Goose, chicken, and duck feathers and downs are primarily to be considered, while pigeon, turkey, and swan feathers are rarely the cause of allergy. Feathers are extensively used, of course, in pillows, cushions, quilts, mattresses, and upholstery. It is interesting that in many cases of rhinopathy with demonstrable hypersensitiveness to feathers, the patients can sleep on feather-stuffed pillows without symptoms, but have attacks of sneezing when making their beds. In occasional instances, asthmatics show themselves to be hypersensitive only to the contents of their own pillows. In such cases one must suspect

that the hypersensitiveness is not to the feathers themselves, but rather to molds or mites or even bacterial contamination in the feathers. Some patients manifest their hypersensitiveness to the contents of their pillows only at certain times; this may be explained by the fact that a certain amount of humidity is necessary if molds are to multiply or organic substances to decay under the influence of bacterial growth. Finally, the allergic condition may also be attributed, in occasional cases, to feathers worn on hats or other clothing.

Living fowl and birds have also proved to be the causes of certain cases of asthma or rhinopathy in individuals who raise or handle poultry. Furthermore, a few cases of asthma have been reported as due to canaries and parrots, as well as to pigeons or sparrows nesting under the gables of the patient's house.

However, not only epidermal substances from animals, but also those from *human beings* can, under certain circumstances, constitute the causal agents. This occurs sometimes among hairdressers, barbers, and wig-makers. The writers have observed several cases in which definite attacks of rhinorrhea were brought on by combing the hair on a scalp affected with dandruff. In another case of the senior author's, an attack occurred every time the patient slept with his wife; these manifestations were shown to be due to the patient's hypersensitiveness to his wife's dandruff. After the latter condition had been cleared up, the asthma attacks ceased.

2. ANIMAL EMANATIONS

It has been proved by a great number of observations that some patients develop allergic symptoms from the mere odor of certain animals, without coming into actual contact with them. The animals involved in these cases include horses, cattle, dogs, cats, monkeys, sheep, mountain goats, hares, rabbits, guinea pigs, rats, mice, hens, and even bees, toads, and eels. For some persons allergic to the smell of dogs, the proximity of a person owning a dog is a sufficient stimulus to provoke an attack. De Besche⁵⁹² studied this ques-

⁵⁹¹ MOLL, H. H.: *Lancet* 1: 1540, 1933

⁵⁹² BESCHE, A. DE: *Acta med. Scandinav.* 92: 209, 1937.

tion experimentally. He extracted the characteristic odorous substance from horse urine, and placed an open bottle of it in a roomful of "horse asthmatics." Most of them promptly developed their asthma.

A case treated by the senior author illustrates the degree that such a hypersensitivity can reach. A woman patient 30 years of age regularly developed extensive angioneurotic edema, usually followed by anaphylactic collapse, when she passed a street in which a fish market was located. A similar instance is that of a farmer who regularly suffered an attack of asthma when a west wind set in and carried the smell of horses from a stable located a few hundred feet to the west of his house.

In general, persons hypersensitive to the odor of animals are also susceptible to direct contact with them. However, there are certain exceptions. For instance, it is reported that patients allergic to horses may not be hypersensitive to horse dander and hair. This suggests that the allergens are the volatile substances produced by the sweat and apocrine glands of the skin. Despite absence of the proper chemical experiments, the authors are of the opinion that these emanations contain, among other substances, some highly specific proteins that are the allergenic agents.

Finally, this group also includes those patients who are so hypersensitive to animal protein that even the smell of a specific animal food elicits symptoms identical with those appearing after its actual ingestion. In this connection, Sutton, as well as Decker has described patients hypersensitive to egg white in whom anaphylaxis developed when they were merely present in a room where an egg was being opened. Kaemmerer reported the appearance of swelling of the eyelids and conjunctivitis from the mere smell of fish. Lewis and Grant even observed edema over the entire body in such a case. Boss and the present writers saw typical asthmatic attacks and urticaria in similar instances. Feinberg and Aries reported a case of asthma due to the odor of cooking shrimps, and Randolph⁷⁴ a case of migraine which could be evoked by the odor as well as the ingestion of milk. Horesh⁸⁹ has emphasized the significance of foods as

inhalants, particularly in infantile dermatitis, and has pointed out that apparent failure of elimination diets may be due to exposure to the food allergen by this route. He reported a series of cases in which pruritus recurred or the dermatitis was exacerbated in the proximity of fully dressed fowl, when eggs were opened or cooked, and when fish, pork, or bacon was fried. Oliver⁸⁴ has described two similar cases due to the odor of eggs. It would appear to be sound advice to keep food allergic infants and children out of the kitchen.

As an enlightening example of what the authors would like to term "materialization of scents," we may mention an observation of Vaughan's.²¹ A man hypersensitive to salmon was eating a salmon croquette to which he promptly reacted with an attack of asthma. The cook took the remaining croquettes to the refrigerator, where he stored them near a package of butter, so that on the next day the butter tasted of salmon, on eating some of this butter, the patient had another attack.

3 INSECTS

Allergy due to inhalation of air borne insect fragments is comparatively rare. Of the twenty three important orders of insects, only three would appear at present to be of major importance in this respect: the *Lepidoptera* (moths and butterflies), the *Trichoptera* (caddis flies), and the *Ephemeroidea* (May flies). The first two are characterized by wings covered on both surfaces with scales or hairs (Fig. 78) of varying shape that are easily rubbed off, either in flight or on the most gentle contact, forming a fine "dust" that is readily wind borne (Fig. 79). In the case of May flies, the mechanism differs in that no insect "dust" is scattered. However, dried fragments of the thin delicate pellicle shed by the insect after the subimago stage of its life are readily windborne and exceedingly abundant in certain vicinities.

Other insects, such as houseflies and bees, lack these characteristics and hence much less frequently cause symptoms of hypersensitivity attributable to such inhalation of fragments. Unrelated forms of insect allergy, such as the bites and stings of flies, fleas,

bedbugs, mosquitoes, and bees are discussed in the chapter on injectants (p 370).

The subject of allergy to insect (both their emanations and their bites and stings) has recently been reviewed by Brown⁵⁹⁸

Parlato⁵⁹⁶ reported in 1929 the first recorded case of coryza and asthma due to the hairs and

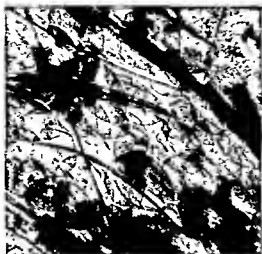


FIG 78 PORTION OF WING OF COMMON CLOTHES MOTH, SHOWING SCALES AND HAIR THAT COVER ITS SURFACE (X 160)



FIG 79 SCALES AND HAIRS BRUSHED FROM WING OF COMMON CLOTHES MOTH (X 160)

scales of caddis flies, also known as sandflies. Skin and conjunctival tests, passive transfer, and clinical exposure all yielded positive findings. Subcutaneous injections of an extract resulted in successful hyposensitization. Parlato⁵⁹⁷ has since recorded a total of 43

cases of asthma and hay fever due to this cause, including 9 patients also troubled by hives and dermatitis. Also in 1929, Figley⁵⁹⁹ reported 4 cases of seasonal asthma, 3 of them associated with hay fever, due to May flies, variously known as shad, lake, or river flies. All the patients had strongly positive skin tests and one was satisfactorily treated pre- and coseasonally. Figley⁵⁹⁹ has more recently reported 40 instances of seasonal hay fever and asthma in which part or all of the symptoms were caused by the May fly. Results of hyposensitization were quite satisfactory.

In 1918 Caffrey, an entomologist working with the New Mexico range moth (*Hemileuca oliviae*), observed in himself and several co-workers that continued contact with the spines of the larvae and the hairs of the adults produced first hay-fever-like symptoms and then violent paroxysms of coughing and wheezing. These observations were later confirmed by Randolph,⁶⁰⁰ who reported similar symptoms in an entomologist, due to inhalation of the dust from the floor of the cage in which these insects were kept. Positive intradermal tests were obtained with extracts of the dust and of the insect eggs, and successful passive transfer tests were performed, indicating the allergenic nature of the covering and spines of the larvae.

Parlato⁶⁰¹ in 1932 demonstrated that emanations of moths and butterflies can act as allergens. The diagnosis was based on the observation of a large number of hairs and scales on glass slides exposed in the patient's home, on the negative results of routine tests, and on the absence of symptoms when the patient was elsewhere.

Wittich,⁶⁰² in studying occupational exposure to allergens in grain and seed mills, found that the Indian-meal moth (*Plodia interpunctella*) of the order *Lepidoptera* produces respiratory allergy owing to the heavy infestation of shelled seed corn with the epithelium of its wings.

Urbach and Gottlieb⁶⁰³ reported asthma and allergic rhinopathy of nine years' duration due to the common or webbing clothes moth

⁵⁹⁸ BROWN, E. A. *Ann Allergy* 2: 235, 1944.

⁵⁹⁹ FIGLEY, K. D. *Am J M Sc* 128, 338, 1929.

⁶⁰⁰ RANDOLPH, H. J. A. M. A. 103: 560, 1934.

⁶⁰¹ PARLATO, S. J. *J Allergy* 3: 125, 459, 1932.

⁶⁰² WITTICH, F. W. *Journal Lancet* 60: 418, 1940.

⁶⁰³ URBACH, F., and GOTTLIEB, P. M. *J Allergy* 12: 437, 1941.

⁵⁹⁶ BROWN, E. A. *Ann Allergy* 2: 235, 1944.

⁵⁹⁷ PARLATO, S. J. *J Allergy* 1: 35, 1929.

⁵⁹⁸ Idem *ibid* 10: 56, 1933.

(*Tineola biselliella*) This allergy was caused by infestation of the patient's home and was entirely relieved on absence from the house. The suggestive history, the positive inhalation and skin tests, and the complete control of symptoms by injections of moth extract justify the designation of this case as one of specific moth allergy. It differs from other cases of moth allergy by reason of the absence of occupational influences.

A variety of other insects have been held responsible for isolated cases of allergy. Two cases of asthma due to the emanations of bees were proved by Ellis and Ahrens.³⁹⁴ Both of these cases were sensitive to the air borne bee emanation, attacks of asthma being initiated when the patients were near bees or near objects that had been in contact with bees. One patient had an attack of asthma following a car ride with a friend. Inquiry revealed the fact that a robe in the car had been used to wrap a hive of bees while transporting them a short time before. Weil³⁹⁵ mentioned a case of hay fever, in a hydro electric dam worker in Alabama, due to dead bodies of tanytarsi midges of the family *Chironomidae*. Asthma resulting from sensitization to the housefly (*Musca domestica*) has been reported by Jameson,³⁹⁶ to the mushroom fly (*Aphrochaeta agarici*) by Kern,³⁹⁷ and to the locust by Ludmer.³⁹⁸ Wittich³⁹⁹ found positive skin reactions to extracts of book lice (*Troctes diutator*) and two cases of allergic rhinitis and asthma,³⁹⁹ in grain and seed mill workers due to the Mexican bean weevil (*Zabrotes subfasciatus*).

Sheldon and Johnston⁴⁰⁰ described an instance of allergic rhinitis and asthma due to hypersensitiveness to beetle (*Coleoptera*) emanations. Way⁴⁰¹ reported asthma caused, in a case of inhalant sensitivity, by the water flea (*Cladocera*), a small animal of the phylum *Arthropoda*. Water fleas are an important food for fishes and the patient acquired his sensitivity while raising fish at home and feed-

ing them water fleas. It should be noted that in contrast to the caddis fly, May fly and moth which are insects, the water flea is a crustacean.

4 MITES

Ancona⁴⁰² observed that 21 inhabitants of an Italian village who had been working for some time at milling grain all became asthmatic at the same time. He was able to ascertain that this sudden allergization was due to the mite *Pediculoides ventricosus*, a parasite of the corn moth, *Tinea granella*, with which the grain in some parts of Italy was infested at the time. The identity of the causal agent was proved by the fact that neither an extract of the flour itself nor of the corn moth evoked any response on skin testing or inhalation, but that extracts of the mites elicited both cutaneous reactions and asthma. These findings were confirmed by van Leeuwen⁴⁰³ both clinically and in animal experiments. He found that when unprepared guinea pigs were confined in a sty containing mite infested grain, they manifested no reaction, but after they had become allergized by being exposed to the mite-infested grain for several days, they began to evince typical asthmatic attacks. Similarly, it is possible to allergize animals by subcutaneous administration of an extract of mite infested grain, and subsequently to provoke anaphylactic shock in them.

According to Dekker⁴⁰⁴ and Haase,⁴⁰⁵ allergy to mites is important in another way. In the course of their investigations these authors found that the dead mites disintegrate into minute particles and that this dustlike substance, carried by the air, readily brings on allergization of the nasal and bronchial mucosa. According to Dekker, vast quantities of mites—especially *Glyciphagus domesticus* and *G. spinipes*—are to be found in old and slightly damp upholstered furniture, while mites of other species—*Tyroglyphus farinae* and *Aleurobius farinae*—may be present in grain (wheat, oats, barley, corn) on seeds (birdseed) in the bowls from which dogs and cats are fed, in straw, on groceries (prunes, figs, dried fruit), in upholstery workshops, in dolls, old books, parchment, and herbarium specimens. It is

³⁹⁴ ELLIS R. V. and AHRENS H. G. *ibid.* 3: 247, 1932.

³⁹⁵ WEIL C. K. *ibid.* 11: 361, 1940.

³⁹⁶ JAMESON H. C. *ibid.* 9: 23, 1938.

³⁹⁷ KERN R. A. *ibid.* 9: 604, 1938.

³⁹⁸ LUDMER N. *Semana med.* 1: 1025, 1935.

³⁹⁹ WITTICH F. W. *J. All. ex.* 12: 42, 1940.

⁴⁰⁰ SHELDON J. M. and JOHNSTON J. H. *ibid.* 12: 493, 1941.

⁴⁰¹ WAY K. D. *ibid.* 12: 495, 1941.

⁴⁰² DEKKER H. *Therap. d. Gegenw.* 19: 7, p. 362.

⁴⁰³ HAASE A. *Ztschr. f. aug. Entomol.* 12: 343, 1927.

always necessary, therefore, to bear in mind that mites may possibly be the causal agents in otherwise inexplicable cases of asthma, especially in workers handling barley, figs, dried fruit, in farmers who store wheat, and in upholsterers. In Holland, according to Meerburg, the mites in old mattress stuffing materials must always be considered as possible inhalant allergens.

5. SILK

Recent investigations have revealed that hypersensitiveness to silk is acquired by inhalation in the majority of cases, and not by way of skin contact. This is true not only in cases of asthma and rhinopathy, but also in certain cases of neurodermatitis and urticaria, according to the reports of Taub and Zakon,¹¹⁴ Figley and Parkhurst,¹¹⁵ and Sulzberger and Vaughan.¹¹⁶ The identity of the causal allergen in these cases of neurodermatitis associated with hypersensitiveness to silk is proved by the appearance of severe itching, violent sneezing, and a watery nasal discharge following insufflation of dry powdered silk protein into the nostrils. In passively sensitized individuals, Sulzberger and Vaughan succeeded in evoking urticarial reactions at the sensitized skin sites twenty minutes after inhalation of a dry silk extract.

Davidson¹¹⁷ recently reported the interesting case of a 30 year old Negress who had severe asthma each weekend, requiring hospitalization and oxygen therapy. Investigation revealed that it was due to silk dresses worn only at that time of the week, and discontinuance of this practice resulted in complete freedom from symptoms.

Silk is, of course, the thread spun from a silkworm's cocoon. These threads are twisted; the long-fibered ones are used for the manufacture of cloth, while the broken and tangled shorter fibers (so-called silk floss) are spun. Silk is most extensively employed for men's and women's underwear, night clothes, stockings, socks, neckties, veils, and other apparel. Silk is sold under a wide variety of trade names,

including satin, foulard, faille, crepe de chine, pongee, taffeta, georgette, jersey, etc. Silk floss is used for stuffing pillows and quilts. Individuals who are hypersensitive to silk can, of course, tolerate artificial silk, such as rayon.

Divergent views are held as to the nature of the silk allergen. Three possible identities seem worthy of consideration: (1) the silk fiber itself; (2) the gum or glue (sericin) contained in raw silk; (3) the silkworm. Milford, also Parlato and Swarthout, found that the silkworm pupa contains ten times more allergen than does the cocoon. Clarke and Meyer, also Figley and Parkhurst, are of the opinion that the gum or glue is the antigen. But Vaughan¹¹⁸ rightly points out that "in view of undoubted sensitization to silk cloth which contains no pupa and relatively little sericin, some of the excitant must persist in finished silk."

Silk extracts for testing purposes should be derived from raw silk or from silkworms directly.

6. GLUE, BOVE DUST, PEPTONE, PARASITES

Although it is true that glue generally exerts its allergenic effect in direct contact, a few cases have been reported (Andrews and McNitt¹¹⁹) in which asthmatic attacks were elicited by proximity to glue (e.g., working in a drafting room or an art school). Hypersensitiveness to fish glue is often encountered among individuals allergic to fish. Fish glue is prepared from the head, bones, and skin of many species, including cod, haddock, hake, pollack, and cusk. Glue is used in the manufacture of a wide variety of articles—furniture, toys, paper, bookbindings, wallpaper, labels, leather goods, as well as in fabrics and numerous other items.

Antona¹²⁰ and Weston¹²¹ have reported 2 cases in which asthma was due to hypersensitiveness to powdered cuttlefish bone (sepia). One of these patients was employed as a gold worker, the other in a jewelry factory. The diagnosis was made on the basis of the histories, skin tests, and passive transfer, and of the asthmatic attacks elicited by injections of sepia extract, it was further confirmed by com-

¹¹⁴ TAUB, S. J., and ZAKON, S. J. *J. Allergy* 5: 53, 1933

¹¹⁵ FIGLEY, K. D., and PARKHURST, H. J. *ibid* 5: 60, 1933

¹¹⁶ SULZBERGER, M. B., and VAUGHAN, W. T. *ibid* 5: 351, 1934

¹¹⁷ DAVIDSON, M. T. Letters, Internat. Conf. Club of Allergy, Series 8: 166, 1945

¹¹⁸ ANDREWS, G. C., and MCNITT, C. W. *J. Allergy* 3: 30, 1931

¹¹⁹ ANTONA, G. *Polichnico (sez. prat.)* 29: 1452, 1922

¹²⁰ WESTON, C. G. *J. Allergy* 2: 37, 1930

plete freedom from symptoms after change of occupation. Cuttlebone powder is used for a variety of purposes for engraving and molding of jewelry, for filtering chemical products by piano manufacturers, as the basis of metal cleansers, and as an addition to bird and poultry food.

Stoetter⁹¹ has reported a case of marked hypersensitiveness to peptone powder, a substance employed in the preparation of culture media. A laboratory assistant in a hygiene institute regularly had severe attacks of asthma when he handled this powder, but liquid peptone was tolerated perfectly. The degree of hypersensitiveness in this case was demonstrated by the fact that injection of 0.2 cc of staphylococcus vaccine containing about 0.000001 Gm of peptone (from the culture medium) evoked a severe anaphylactic shock accompanied by urinary incontinence and acute emphysema of the lungs.

In contradistinction to allergic manifestations due to infestation, which will be discussed in chapter XIX, the inhalation of the protein or products of parasites can give rise to sensitization. Thus, not a few physicians, biologists, and laboratory workers have been known to have acquired asthma, rhinopathy, conjunctivitis and migraine after prolonged exposure to intestinal worms. How difficult it sometimes is to establish the relationship is illustrated by a case reported by Heggin.⁹² A woman employed in a slaughterhouse developed asthma that was found to be due to the ascarides harbored by the animals. The asthmatic symptoms ceased as soon as she abandoned this occupation. There were recurrences, however, that were attributable to contact with her husband, a butcher, who was regularly in contact with ascaris-infested animals. Only after her husband had been persuaded to change his clothes regularly before coming home, did her asthma finally disappear. Subsequently, symptoms recurred and were found to be due to ascaris infestation in her son.

C AGENTS OF VEGETABLE ORIGIN

1. POLLEN

Ever since Blackley⁹³ the brilliant English homeopathist performed his epoch-making experiments on himself in 1873, it has been shown that plant pollens are the principal cause of the symptom complex called hay fever. Typical manifestations appeared when he and other predisposed individuals sniffed the pollens.

Before entering into discussion of the morphologic, physical, chemical and immunologic characteristics of pollen, it might be useful to delineate briefly the essentials of flower structure and of the process of pollination. The

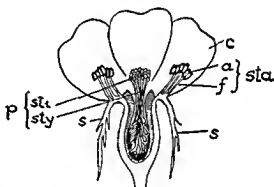


FIG. 80. DIAGRAM OF LONGITUDINAL SECTION OF PERFECT FLOWER (DOG ROSE)

a = anther c = corolla f = filament p = pistil s = sepals sta = stamen stg = stigma sty = style

reproductive apparatus of all flowers consists of a male element, or stamen, and of the female part, or pistil. When both are present in the same flower, it is regarded as a 'perfect' type, but when either one is absent, the flower is termed 'imperfect'. The stamen consists of the filament and the anther (FIG. 80), in which the pollen grains—which correspond to the sperm cells of animals—are formed and temporarily stored. The pistil is composed of a swollen lower part, the ovary, containing the ovules (from which the seeds develop), and a longer or shorter slender part, the style, the

⁹¹ STOETTER, G. *Klin. Wchnschr.* 16: 1180, 1937.

⁹² HEGGIN, O. *Schweiz. med. Wchnschr.* 59: 11, 1939.

⁹³ BLACKLEY, C. H. *Experimental Researches on the Cause and Nature of Catarrhus Aestivus*. London, 1873.

apical end of which (the stigma) is used as a receptor organ for the pollen.

When an immature anther is bisected (FIG. 81), the four pollen sacs are clearly seen as individual sections or compartments. Before the stamens reach maturity, the four sacs are completely separate. Later they merge into two groups of two each.

The function of the pollen is to fertilize the ovules, thereby producing seeds. The pollen grains thus have to be transferred from the anther to the stigma. This process is called pollination or anthesis. Once upon the stigma the pollen begins to germinate, producing the

other words, there is likely to be a great quantity of pollen from wind-pollinated plants, and a much smaller quantity from plants whose pollination is accomplished by the instrumentality of insects. This is explained by the fact that the wind-borne pollens are especially light, dry, and buoyant, whereas the insect-borne pollens are relatively heavy and sticky, adhering the more readily to the wings and other parts of the insect, and thus facilitating the transportation of the pollen to female blossoms. For the purpose of attracting insects to the insect-pollinated flowers, nature has endowed them with bright colors, conspicuous scents, and nectar-producing glands.

Transference by birds or by water is relatively rare, and does not play a significant rôle as far as pollen allergization of man is concerned. Insect-borne pollens are, in general, far less abundant than wind-borne pollens, and for that reason too are of less importance as hay fever excitants. This does not mean, however, that they can be completely ignored—as is so often the case. The writers have observed a number of instances in which failure of therapy directed against sensitivity to a wind-borne pollen was due to ignorance of the fact that there also was a hypersensitivity to goldenrod, dahlia, or daisy. In these cases the patients were rapidly freed of their symptoms when these insect-borne pollens were included in the treatment extract.

The gross appearance of pollen is that of fine powder. The color usually ranges from light to dark yellow, but other colors are also encountered, as red, blue, green, violet, orange, purple, white, there is also a colorless type. The morphologic characteristics depend to some extent on whether the pollen is in a dry state or has been allowed to absorb moisture. Most pollen granules are oval (FIG. 82), ellipsoidal, or spherical structures composed of an outer cell wall (exine), an inner wall (intine), and the cytoplasm (FIG. 83). The latter is the bearer of the pollen's function, the pollen tube grows out of it at the time of fertilization. Depending on the species of the pollen, there are one or more openings (pores) through which the pollen tubes pass on germination (FIG. 84).

The size of the pollen grains varies consider-

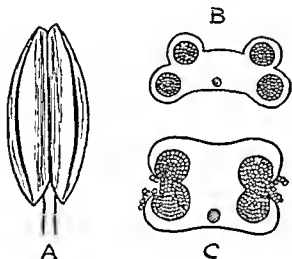


FIG. 81 IMMATURE FLOWER

A = intact anther B = cross section, pollen sacs distinctly separated C = fusion of adjoining pollen sacs and discharge of pollen

pollen tube which contains the male sex cell. The pollen tube grows through the tissue of the style and reaches the ovule. Here fertilization takes place. In most instances the pollen is carried from one flower to another one—cross-pollination. Such transfer of the pollen can be accomplished by animals (insects, birds, small mammals), water, or wind. Only wind-borne pollen has a relationship to hay fever and can come into contact with the hypersensitive structures of human beings.

The quantity of a specific kind of pollen in the air at a given time depends on the abundance of the plant and its rate of pollen production, as well as on the mode of transfer: in

ably The forget me not (*Myosotis*) family have about the smallest pollen grains (6 microns), the pumpkin (*Cucurbita pepo*)

about seven times the size of a red blood corpuscle (7.5 microns)

In the plants evoking hay fever, the smallest pollen grains are those of the *Ambrosiaceae* (*Compositae*) measuring 18 to 24 microns (Fig 85) next in size are those of the grasses, with an average size of 40 to 50 microns, and the largest are those of corn with a diameter of 80 to 90 microns. The weight of pollens also varies considerably. 1 cc of corn pollen weighs 0.71 Gm, 1 cc of timothy pollen 0.64 Gm, and 1 cc of the ambrosia pollen (e.g., *Ambrosia elatior*) 0.30 Gm (Duke²⁰⁰). Durham²¹ has more accurately determined the specific gravity of pollens by various methods,



FIG 82 POPLAR POLLEN ON VASELINE (X 330)
(Courtesy Dr N Schaffer)



FIG 83 BIRCH POLLEN (X 1170)
E = exine I = intine P = pore
Pl = cytoplasm

family have about the largest (220 microns). On the average, pollen grains are about 50 microns in diameter that is to say, they are



FIG 84 BIRCH POLLEN (X 300)
t — pollen tube extrusion of protoplasm

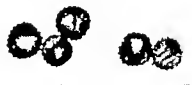


FIG 85 POLLEN OF GIANT RAGWEED (*Ambrosia trifida*)
(X 520)

attempting to eliminate the empty space around the granules permitted in the above figures, and taking into consideration the contained moisture. He estimates that of dried ragweed pollens at approximately 0.5 grass pollens 10, and tree pollens 0.9.

The pollens that evoke hay fever are morphologically not strikingly different from those of other members of the vegetable kingdom. Only those who are well versed in botany will be able to differentiate microscopically between the pollens of trees, grasses *imbrosiaceae*, chenopods, amaranths, and other genera.

The appearance of the outer cell wall is

characteristic for each of the plant groups mentioned above. Thus, the grass pollens have a smooth surface (FIG. 86); those of the



FIG. 86 RYE GRASS POLLEN ON VASELINE (X 550)
(Courtesy Dr N Schaffer)



FIG. 87. WHITE OAK POLLEN ON VASELINE (X 550)
(Courtesy Dr N Schaffer)

ragweed family are distinguished by numerous small spiny projections, or spicules; other families, by peculiar reticulations and sculpturings on their surfaces (FIG. 87). The rela-

tive luminescence of the pollens in ultraviolet light is another criterion that is helpful in differentiating between the various kinds of pollen, as well as in detecting signs of pollution or adulteration. This test is best performed with the quartz lamp or with the Haitinger fluorescence apparatus (Urbach^{92a}).

Which of the pollen's chemical components possesses the capacity of allergizing? Despite all the experimental investigations along this line in the past few years, a definite answer is not as yet available. The first widely entertained view was—and on the basis of more recent studies, it is again receiving support—that the proteins of the pollen are responsible for its allergenic action.

Dunbar long ago determined that the outer shell of the pollen grain is inactive, and that the allergenic factor is to be found somewhere inside the shell. It has frequently been observed that no reaction whatever results from the application of old pollens to the nasal mucosa or conjunctiva, while these same pollen grains elicit an extraordinarily severe hay fever response after being crushed and ground (i.e., after the contents of the shell have been released).

It was also known to Dunbar that extraction of pollens with physiologic salt solution and subsequent precipitation with alcohol yield a substance that exerts a specific exciting effect when applied to the mucosa, even in minute traces. This substance is thermostabile and insoluble in acids. At a temperature of from 80 to 90 C., however, at which almost all proteins become coagulated, a solution of this substance loses about 25 per cent of its allergenic capacity; on prolonged cooking it loses about 75 per cent. These facts would seem to exclude the possibility of a relationship of the active substance to the pollen protein. Of further significance is the relatively high resistance of the substance to digestive enzymes. Several hours of treatment with pepsin, hydrochloric acid, and trypsin are required before this substance begins to disintegrate, while at least some of its effectiveness as an excitant remains even after days of digestion (Prausnitz^{92b}).

^{92a} URBACH, E. *Das Heufieber und seine Behandlung*. Vienna, Maudrich, 1917.

^{92b} PRAUSNITZ, C. *Handb d path Mikroorg* 3 (pt 1) 125, 1930.

More detailed analysis of pollen protein by Prausnitz indicated that when rye pollen protein is fractionated the allergenic substance stays with the albumin portion. On the other hand, the senior author⁹²⁷ on the basis of chemical investigations and of experimental tests on patients concluded that the allergenic principle appears to be associated with the globulin and not with the albumin fraction. More recent fractionation of ragweed pollen by Cohen and Friedman⁹²⁸ likewise yielded a purified globulin which reacted specifically with an antibody peculiar to itself, however, all protein fractions including a crystalline one, were highly active in direct skin tests, in neutralizing capacity, and in precipitin reactions with the serum of rabbits allergized with ragweed pollen extract.

On the basis of careful chemical analyses many authorities, including Caulfield, Cohen, and Eadie,⁹²⁹ Farmer Loeb,⁹³⁰ and Stull Cooke and Chobot,⁹³¹ and many others emphatically hold that the allergenic factor in the pollen is of protein nature.

Against this assumption, however, are the facts that the allergen is trypsin resistant and dialyzable—which cannot be true of a protein (Walzer and Grove,⁹³² Grove and Coca⁹³³). An additional point is that relatively little of the allergenic effectiveness is lost by heating to from 80 to 90 C. or even by brief cooking (Gutmann). On the strength of these arguments as well as on the basis of their own investigations, a number of authors besides Grove and Coca—particularly Black⁹³⁴—adopted the view that the allergen is a polysaccharide that may be conjugated with a protein. Moreover ultracentrifugation of ragweed pollen extracts by Sanigar⁹³⁵ indicated molecular weights considerably less than those of proteins. By absorbing the non specific nitrogenous portions of pollen extract on Norite A, Brown and Benotti⁹³⁶ concluded

that the true antigen is not an albumin but a small molecule containing a carbohydrate fraction and an alpha amino group. In fact Caulfield⁹²⁸ achieved therapeutic relief by administering the carbohydrate fraction of a ragweed pollen extract. However Harley⁹³⁷ and Service⁹³⁸ found the skin reactive potency of the carbohydrate fraction of timothy pollen and of several western pollens to be slight or nil. According to Newell⁹³⁹ the allergenic activity of pollen is probably shared by several substances that are all of complex chemical nature. Some of them are apparently carbohydrates others resemble proteins.

However, in all these studies, consideration must be given to the question as to whether or not the proteins can really be completely separated from the carbohydrate complex and whether or not present chemical methods are capable of demonstrating minute traces of protein, that are still capable of evoking allergic reactions. Thus Urbach and Fasal⁹⁴⁰ definitely demonstrated that none of the present chemical methods ordinarily used will detect the presence of protein in a dilution of 1:100,000 while in extremely hypersensitive human beings biologic methods (e.g., skin tests) will readily demonstrate proteins in dilutions as high as 1:1,000,000,000. In view of this the tested substance may still contain appreciable amounts of specific protein. These biologic and chemical investigations must be borne in mind when considering claims that all protein was removed from a substance, based merely on the fact that chemical reactions were negative. As long as negative results are not obtained on skin testing very hypersensitive individuals with the given substance it is not permissible to rule out the possibility that residual traces of protein are the responsible agents.

The view that the allergenic factor is contained in the pollen oil is held by Milford⁹⁴¹. He bases his opinion on the fact that patients with fall hay fever manifest a typical urticarial reaction to cutaneous or intracutaneous application of the oil of ambrosia pollen. More

⁹²⁷ URBACH E. *Klin. Wchnschr.* 12:1797 1933.

⁹²⁸ COHEN M. B. and FRIEDMAN H. J. *J. Allergy* 14:368 1943.

⁹²⁹ CAULFIELD A. H. W., COHEN C. and EADIE G. S. *J. Immunol.* 12:153 1926.

⁹³⁰ LOEB L. F. *Klin. Wchnschr.* 9:890 1930.

⁹³¹ STULL A., COOKE R. A. and CHOBOT R. J. *Allergy* 3:341 1932.

⁹³² WALZER M. and GROVE E. T. *J. Immunol.* 10:463 1925.

⁹³³ BLACK J. H. *J. Allergy* 3:1 1931.

⁹³⁴ SANIGAR B. *J. Franklin Inst.* 230:781 1940.

⁹³⁵ BROWN E. A. and BENOTTI N. *Oh. State M. J.* 38:1011 1942.

⁹⁴⁰ CAULFIELD, A. H. W. *Proc. Soc. Exper. Biol. & Med.* 31:573 1934.

⁹³⁷ HARLEY D. *Brit. J. Exper. Path.* 18:460 1937.

⁹³⁸ SERVICE W. C. *Colorado Med.* 34:468 1937.

⁹³⁹ NEWELL J. M. *J. Allergy* 13:177 1942.

⁹⁴¹ MILFORD E. L. *ibid.* 1:331 1930.

over, when the fat is completely removed from an oily extract of ambrosia pollen, it is impossible to elicit any kind of skin reaction with what is left. Finally, no more than a faint reaction can be evoked with an aqueous extract obtained by washing the fat with physiologic salt solution; the fat itself, however, is strongly active.

Prausnitz and Benjamins have taken an intermediate stand with regard to the chemical nature of the pollen allergen. Prausnitz^{92b} holds that the hay-fever-eliciting component of the pollen is a relatively simple substance that is somehow—either chemically or by adsorption—connected with the albumin molecule. According to Benjamins,⁹¹ the specific action of pollen extracts is associated with a small-molecular group, and in order to become operative this group requires activation by other bodies, such as a colloidal protein molecule. Harsh and Huber^{92c} found, contrary to Grove and Coca, that digestion of pollen caused a marked loss of allergenic activity, and concluded that the major portion of the antigenicity of ragweed pollen is due to a digestible protein, or to some substance inseparably associated with it, or to some substance active only in the presence of protein. However, investigations by Roth and Nelson⁹³ have shown that while the small-molecular fraction contains the skin-reactive principle, the large-molecular fraction is endowed with the anaphylactogenic and precipitinogenic properties.

Much of this confusion concerning the chemical nature of pollen antigen may be accounted for on the following basis: Newell's^{94a} electrophoretic studies of fractions separated from extracts of ragweed pollen showed that no available chemical means of fractionation yields even approximately a pure chemical substance.

Recent painstaking analyses by Rockwell^{95a} have yielded from crude ragweed pollen extract a major antigen of marked skin reactive, animal sensitizing, and therapeutic properties, which he refers to as Fraction 1, and which corresponds rather closely to similar fractions

previously identified chemically by Stull, and electrophoretically and ultracentrifugally by Abramson and their co-workers. This substance has a molecular weight of 4496.08, an empirical formula of $C_{293}H_{319}O_{70}N_{23}S_1$, and is a complex each molecule of which contains one molecule of flavonol-pigment (isorhamnetin), one molecule of pentose (arabinose), and two polypeptide molecules. The two polypeptides contain an aggregate of 28 amino acids of which 4 to 10 are basic amino acids, and a large percentage of dicarboxylic-amino acids. The suggested structural formula of this fraction is believed to be as depicted in either (a) or (b) in Fig. 88.

Rockwell^{95b} has separated four other active components from ragweed pollen, all consisting of flavanol-carbohydrate-peptide complexes, with the flavanol-glucoside being combined to the peptide by an ester linkage. He consequently favors the concept that antigenicity of pollen is dependent on the presence of the carbohydrate component.

These questions as to the identity of the chemical substance with which the allergen is associated have been given detailed consideration here because an answer to the problem is of special importance in deciding which chemical component of the pollen should be used in therapy. Although considerable evidence favors the protein nature of the pollen allergen, in the present state of knowledge one cannot definitely rule out the possibility that the carbohydrates or oils (fats) participate. Consequently, the use of extracts of the whole pollen seems most likely to assure therapeutic success.

A few authors have with satisfactory results employed extracts of other parts of the plants (Urbach⁹⁷). That hay fever patients react to extracts of stems, which do not contain pollen, and sometimes also to extracts of blades of grasses, was first demonstrated some time ago by Duke and Durham,⁹⁷ as well as by Benjamins, Griebel, Gutmann, and Vallery-Radot. According to Farmer-Loeb, on the other hand, it is impossible to elicit cutaneous reactions with seeds of the same grasses, the pollens of which regularly produce positive skin reactions. However, our own investiga-

⁹¹ BENJAMINS, C. E. *Acta oto-laryng.* 24: 153, 1936.

^{92b} HARSH, G. F., and HUBER, H. L. *J. Allergy* 14: 121, 1943.

^{92c} ROTH, R. R., and NELSON, T. *ibid.* 13: 233, 1942.

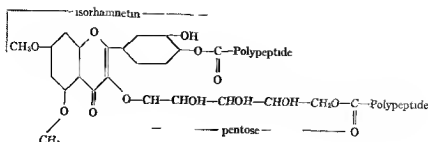
⁹³ NEWELL, J. M. *ibid.* 14: 444, 1943.

^{94a} ROCKWELL, G. E. *Ann. Allergy* 43: 1943.

^{95b} *Ibid.* Ohio State M. J. 39: 128, 1943.

⁹⁷ DUKE, W. W., and DURHAM, O. C. *J. A. M. A.* 82: 939, 1924.

(a)



(b)

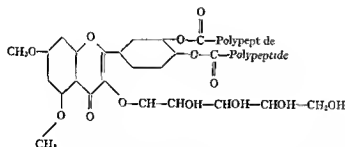


FIG 88 SUGGESTED FORMULAS FOR THE MAJOR ANTIGEN (FRACTION I) OF RAGWEED POLLEN (ROCKWELL²⁴⁰)

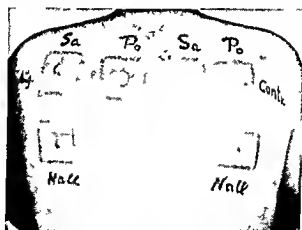


FIG 89 DEMONSTRATION OF CLOSE IMMUNOLOGIC RELATIONSHIP BETWEEN PROTEINS OF GRASS SEED AND OF GRASS POLLEN

Evidenced in passive transfer test by positive reaction to seed extract in skin sites prepared with serum from pollen allergic patient. Three sites at left were prepared with serum of patient allergic to June grass three at right with nonallergic serum. Twenty-four hours later injections were made as follows: seed extract (Sa), pollen extract (Po), normal saline solution (NaCl). Thirty minutes later there were equal reactions to seed and to pollen extract in sites prepared with antibody containing serum while all four controls were negative. This proves allergenic identity of seed and pollen of same species.

tions²⁴⁸ have shown that there is an immunologic relationship between pollen protein and seed protein digest. This is proved by the fact that skin sites prepared with the blood serum

of patients allergic to pollen react to seed protein digest (Fig 89)—showing that the two must be biologically closely related. Moreover, the senior author²⁴⁹ has demonstrated in

animal experiments that (1) seed digest will give skeptophylactic protection against anaphylactic shock from pollen protein, and (2) injection of pollen extract will produce lethal shock in animals allergized to seed digest. This biologic relationship between pollen and digested seed protein is the basis of the method, introduced by us, of oral grass seed treatment of individuals hypersensitive to pollen, and also explains the success of this therapy.

Another important question concerns the allergenic specificity of the pollens of various species of plants. The investigations of Berger and Hansen⁵⁰ indicate (1) the strict specificity of the various families of plants, (2) the probable existence of specificity of the various genera within the same plant family, and (3) the close antigenic interrelationship of the various species of the same plant genus.

In order to determine the biologic identity of the pollens of two species of plants—for example, giant ragweed (*Ambrosia trifida*) and low ragweed (*Ambrosia elatior*)—the following criteria may usefully be employed:

(1) Skin sites that have been passively allergized by the Prausnitz-Kuestner method, and then desensitized with one of the two extracts, must also prove to be insensitive to the other (Coca and Grove⁵¹, Stull, Cooke, and Chobot⁵²). (See exhaustion test, p. 114.)

(2) Neutralization *in vitro* must be demonstrable—i.e., a mixture of the serum of an allergic individual with an aqueous solution of one of the two pollen proteins should be incapable of sensitizing a skin site (Walzer and Bowman). (See cross-neutralization test, p. 114.)

(3) It should be possible to provoke an anaphylactic shock with one pollen extract following allergization of the animal with the other (Urbach and Wolfram).

(4) It should be possible to prevent anaphylactic shock in an animal allergized with one pollen extract by means of skeptophylactic pre-administration of the other pollen extract (Urbach and Wolfram⁵³).

By means of the methods just mentioned, it is possible to determine a fact of great practical

therapeutic significance—namely, that the pollen antigens of certain species of plants are biologically identical. This demonstration was made with regard to *Ambrosia trifida* and *A. elatior* by Brown,⁵⁰ Stull, Cooke, and Chobot,⁵² and others. Simon⁵⁴ found that while ragweed-sensitive patients have skin reactivity to both dwarf and giant ragweed species, as well as to the pollens of botanically related species, it is possible by antibody neutralization studies to determine which is the actually sensitizing allergen. He concluded that the pollens of the ragweeds and their botanic relatives (the composites) contain, in addition to species-specific allergens, multiple common allergenic components which vary in their distribution among related species. A person exposed simultaneously to a group of allergens may become sensitized to certain members of the group and not to others, while another person may acquire sensitivity to different members of the group. On the basis of their experimental investigations, Stull, Cooke, and Barnard⁵⁴ believe that the active substance in the pollens of timothy (*Phleum pratense*), orchard grass (*Dactylis glomerata*), June grass (*Poa pratensis*), redtop (*Agrostis alba*), and rye (*Secale cereale*), is one biologically identical albumin, common to all. According to Piness and Miller,⁵⁵ every member of the grass family possesses a specific allergen—which is, however, to a certain extent related to allergens of every other member of the same family. In this regard it constitutes both an antigen and a metantigen, according to our terminology.

Turning now to the quantitative aspects, credit must be given to Blackley⁵² for establishing how many—or, rather, how few—pollen grains there must be in the air to provoke an attack in a hay fever patient. In experiments on himself, he found that he remained free from symptoms when a glass slide covered with a film of glycerin showed a total of less than 20 pollen grains per square centimeter in twenty-four hours; when the rate was 25 grains in twenty-four hours, he was con-

⁵⁰ BERGER, W., and HANSEN, K. *Deutsches Arch. f. klin. Med.* 170: 458, 1931.

⁵¹ STULL, A., COOKE, R. A., and CHOBOT, R. *J. Allergy* 3: 120, 1932.

⁵² BROWN, AARON. *J. Immunol.* 13: 73, 1927.

⁵³ SIMON, F. A.: *J. Exper. Med.* 77: 185, 1943.

⁵⁴ STULL, A., COOKE, R. A., and BARNARD, J. H. *J. Allergy* 3: 352, 1932.

⁵⁵ PINESS, G., and MILLER, H. *ibid.* 2: 73, 1931.

scious of manifestations of mild irritation of the nose, and when the concentration was 54 to 66, there were severe attacks. Or putting it in other words in an individual hypersensitive to English rye grass (*Lolium perenne*) for example pollen grains weighing at least 0.00008 grain are required to elicit manifestations, and a weight of at least 0.0001 grain is necessary to provoke a severe attack. It may be of interest to state that one grain or 0.06 Gm of English rye grass, for instance, contains 6,000,000 pollen grains, or 100,000,000 pollen grains per gram. Dunbar completely confirmed Blackley's findings. He found that from 2 to 3 rye pollen grains sufficed to cause specific irritation of the conjunctiva of a highly hypersensitive hay fever patient, and the weight of 1 rye pollen grain is approximately 0.000033 mg (1/1,800,000 grain). Moderately hypersensitive hay fever patients manifest symptoms on exposure to from 40 to 50 pollen grains, while in the case of highly hypersensitive individuals no more than 3 to 4 are required, according to the experimental investigations of Prausnitz.

The enormous amount of grass pollen in the air at the time of maximum pollination was calculated by Prausnitz.⁹⁶ About 5,000,000 to 10,000,000 pollen grains settle on a surface of 1 square meter in twenty-four hours. But this figure is really nothing in comparison with the number of pollen grains from weeds. Thommen⁹⁷ figured that a single giant ragweed plant yields 8,000,000,000 pollen grains in five hours of active pollination. An average empty city lot overgrown with ragweed produces 100 ounces of pollen in one season. This amounts to no less than 60 pounds per acre. According to Durham, approximately 1,000,000 tons of ragweed pollen are produced in the United States each season.

The immense profusion of pollen dissemination is well illustrated in tales of historic and geographic interest from widely separated portions of the world at different times. Various referred to as "golden rain," "yellow snow," and "sulfur showers" this phenomenon has been reported from the Basque country, the Alps, Inverness, and the forests of Oregon,

and may cover the ground to a depth of one half inch. Buoyant pollen falling on lakes may form long rafts many yards in length. Such falls usually come from pine fir and related trees. Since each pollen granule is of microscopic dimensions the untold billions involved can scarcely be imagined. Although these species are of no clinical significance, huge invisible clouds of ragweed and other pollens are transported long distances by the winds of both the lower and upper air levels. The pollination of the paper mulberry tree is actually visible as a smoke like puff.

Interesting data on the quantity of pollen at various air levels are supplied by Scheppegrell⁹⁷ who made an airplane ascent to carry out his painstaking observations. He reports that at a height of 130 to 1,300 meters the pollen content of the air is about the same as at ground level, while the number of pollen grains begins to decrease gradually at a height of from 2,000 meters to 2,300 meters, from which point on the decrease is sharp. Naturally these figures do not apply to high altitude valleys, where, at a height of 2,000 meters, for example, about the same quantity of pollen is to be found in the air although later in the season.

The effect of weather conditions on pollen movement is best shown by data collected by O. C. Durham on two flights across Ohio. A heavy cloud layer of ragweed pollen blanketed northern Ohio on August 16, 1938. It was first encountered at an altitude of 5,000 feet on the descent to Cleveland. At 4,000 feet the slide caught 99 ragweed granules per square centimeter, at 3,400 feet, 640, at 2,700 feet, 675, and at the decreasing level from 2,000 feet to the ground the count dropped to 330. On the ascent from Cleveland, as the plane proceeded eastward the heavy pollen layer disappeared at 3,000 feet, the last traces of ragweed were observed at 6,500 feet. The sky was clear and there was a south wind. Two days later, with a clear sky and a light breeze from Lake Erie, the average ragweed concentration found in the vicinity of Cleveland was less than 2 per cent of what it had been on August 16.

⁹⁶ THOMMEN A. A. Hay Fever. In Coca A. F. Walker M. and Thommen A. A. Asthma and Hay Fever. Springfield, Ill. Thomas 1931.

⁹⁷ SCHEPPEGRELL W. Hay Fever and Asthma. Philadelphia, Lea 1922.

The relative ease with which pollen is carried by the wind is determined by the size and shape of its grain: the smaller the grain, the more buoyant the pollen. And it is well worth bearing in mind that the capacity of pollen granules for air-borne motion is truly extraordinary—a fact that is of special significance in that it helps us explain many other inexplicable symptoms of hay fever patients. Not even an ocean voyage will guarantee absolute freedom from symptoms, for pollens are not at all unlikely to be carried far out to sea by a land breeze (as was observed by Walshe while crossing the Atlantic). Darwin has reported the fact that pollen can be transported hundreds of miles by the wind. He described how, in St. Louis, Mo., he found the ground literally covered with a yellow layer of fir pollen, and ascertained that it had traveled at least 400 miles in a southerly direction from the fir forests in the north. Vaughan reported that pollens definitely originating in Alaska were found in the states of Washington and Oregon. In 1939, O. C. Durham examined oiled glass slides that were exposed on trips across the Atlantic to Europe and back in an airplane. He reports that pollen was found at altitudes between 2,000 and 8,000 feet, and as far as 275 miles out from land, while at a height of 8,000 feet and more there was practically no pollen, either over land or sea. However, since the plane did not fly at lower altitudes when far offshore, the possibility still remains that pollen may be present "at the bottom of the air" farther out at sea than the slides actually showed.

PLANTS THAT CAUSE POLLINOSIS

In principle at least, hay fever can be caused by any plant that sheds pollen. In practice, however, of the many hundreds of species of trees and thousands of species of grasses and weeds, only relatively few come into consideration as playing a major rôle in the causation of pollinosis. According to Thommen,³⁴⁶ the pollen must have the five following characteristics in order to be of importance in the production of hay fever symptoms: it must be wind-borne, must be produced in large quantities, and must be sufficiently buoyant to be carried considerable distances, and the plant producing the pollen

must be widely and abundantly distributed. But a pollen need not necessarily be a hay fever excitant even if it is wind-borne, abundant, and light, as is the pine pollen, for example. Thommen deduces, therefore, that the pollens causing hay fever must contain a "specific excitant," and in his opinion it is just this as yet unknown, unidentified something that endows the pollen with its capacity to allergize.

Harsh³⁴⁸ has attempted a quantitative estimation of the relative importance of pollinating plants based on the abundance of the species, the amount of pollen produced in a given time per unit area, the period of anthesis, and some factor expressing the ability of the pollen to travel from plant to patient. Many variable factors must be considered which cannot be incorporated into a formula, such as the proximity of the plants to centers of habitation, the prevailing direction and velocity of the wind, the height from which the pollen takes off, the existence of spicules or wings on the pollen, and of course, the changing location of the patient. The relative allergenicity or "toxicity" of each species varies with each patient, and must be separately considered.

While in general Thommen's postulates accord with clinical experience, it must be pointed out that there are some important exceptions. Thus, more recent investigation indicates that plants which are ordinarily insect-pollinated, such as goldenrod, dahlia, and daisy, can under appropriate conditions cause hay fever. This occurs, for example, if the patient lives in the proximity of large plots of these weeds or flowers and a heavy wind is blowing toward his dwelling, or in gardening with plants the pollen of which is insect-borne, and therefore not produced in large quantities and not very buoyant.

Aside from the botanic and geographic conditions governing the local flora, meteorologic factors also play an important rôle. These include, of course, the amount of rainfall, the degree of humidity, the range in temperature, the amount of sunshine, and the wind velocity. Weather conditions directly influence pollination in two ways: by determining the time of onset of flowering, as well as the profuseness of

³⁴⁸HARSH, G. F. *Ann. Allergy* 3: 27, 1945

vegetation and by controlling the amount of pollen that is discharged into the air from day to day. Heavy rainfall prior to the season tends to bring on a luxuriant growth of plants while a drought has the opposite effect. Showers or high humidity during the season temporarily decrease the amount of pollen in the air while strong winds stir up more pollen and drive greatly increased amounts into the atmosphere. In sunny and warm weather the anthers open and discharge copious amounts of pollen. Although the grasses and ragweeds in particular pollinate early in the morning (from 4 to 7 A.M.) many patients experience their most severe symptoms late in the afternoon and after midnight. This is generally explained by the fact that on warm days there is an upward current of air that carries the pollen to a height of from 2 000 to 3 000 feet forming a veritable pollen cloud at about these levels. The cooler temperatures of the evening and night serve to bring the pollen down to earth thus causing the symptoms to appear at these times of the day. Not only the strength of the wind but also its direction is a significant factor. In coastal districts land winds carry large quantities of pollen while winds coming in from the ocean carry few if any. These various atmospheric factors therefore exert definite and far reaching influences and often help to explain strange clinical observations.

Wodehouse⁹⁴⁹ has recently made a great contribution to the field of allergy by presenting in readily available form the requisite botanic facts concerning the hay fever plants of North America including their appearance and distribution. Fogg⁹⁵⁰ has prepared an excellent illustrated guide to assist in the identification of the common weeds of lawn and garden. Information concerning the hay fever producing plants of the rest of the world can be obtained from scattered publications but that relating to Argentina, Uruguay and Brazil may be found in Urbach and Gottlieb⁹⁵¹ Shahon⁹⁵² and Ballestero and Monticelli⁹⁵³.

The following discussion of the plants that produce hay fever will embrace three main groups: trees, grasses and weeds.

It is felt that precise botanic descriptions of the various species and of their pollens would be undesirable here. Such information although essential for the identification of individual plants and of pollens on exposed slides can be readily obtained from appropriate reference books. For the latter purpose reference to the standard works of Wodehouse⁹⁵⁴ and Erdtman⁹⁵⁵ as well as a recent thoroughly illustrated article by the former⁹⁵⁶ concerning the identification of pollen grains will be indispensable. In this as in succeeding sections it is necessary to include the scientific names since the common names are often ambiguous, misleading and overlapping. Moreover the taxonomic nomenclature has the advantage of indicating botanic relationships.

Trees

In general in the United States tree pollens are the cause of spring hay fever the season lasting from March to May or the early part of June although several specific exceptions to these dates will be noted below. In the southern states and in California the season commences a month or two earlier. The pollination period of trees is subject to considerable variation from year to year because of the unsettled meteorologic conditions of the spring. In general a few consecutive days with an atmospheric temperature between 50 and 60 F are required to stimulate anthesis. Most well pollinated trees shed their pollen shortly before their leaf buds open or as the leaves unfold. Many hundreds of different species of trees exist in the United States but many of them are not known to produce hay fever. This is particularly true of course of insect pollinated species such as wild and cultivated fruit trees. Of those that do some are responsible for only sporadic cases due usually to unique conditions of exposure as for example a tree growing just outside a bedroom window.

⁹⁴⁹ WODEHOUSE R. P. *Hayfever Plants*. Waltham, Mass. Chronica Botanica Co. 1945.

⁹⁵⁰ FOGG J. H. JR. *Weeds of Lawns and Gardens*. Philadelphia Univ. of Pennsylvania Press 1943.

⁹⁵¹ URBACH E. W. H. collaboration with GOTTLIEB P. M. *Allergy* (Portuguese edition) translated by Pato Ortiz. Rio de Janeiro Ed. to da Quaresma 1943 pp. 263-6.

⁹⁵² SHAHON H. I. *Compendio de Allergia Clínica*. Buenos Aires Librería Hachette S. A. 1943.

⁹⁵³ BALLESTERO L. H. and MONTICELLI J. V. *Pollenos*. Buenos Aires Hachette S. A. 1943.

⁹⁵⁴ WODEHOUSE R. P. *Pollen Grains*. New York M. G. & H. 1933.

⁹⁵⁵ ERDTMAN G. *An Introduction to Pollen Analysis*. Waltham, Mass. Chronica Botanica Co. 1943.

⁹⁵⁶ WODEHOUSE R. P. *Publication of the U. S. National Academy of Sciences* 8-31 1941.

Although a single tree can shed large amounts of pollen, the individual species almost always have a short pollination season (averaging about two to three weeks); the distribution and frequency of a species are generally limited, and the spring rainfall is likely to precipitate the pollen grains. Hence, tree hay fever tends to be mild and of brief duration. However, it should be noted that the successive or overlapping pollinations of various species of the same genus, such as oaks, or a concomitant hypersensitiveness to several different pollens, as is often the case, may not infrequently give rise to symptoms that persist for a considerable period. Moreover, in most parts of the United States, the pollination of the trees still continues when that of the grasses commences, and a patient sensitive to both may suffer for several months.

As a rule, the Gymnosperms, evergreens, such as pine, spruce, hemlock, fir, cypress, arbor vitae, cedar, and redwood, are less important in this regard than trees and shrubs belonging to the Angiosperms, the higher flowering plants. However, the mountain cedar, an evergreen, constitutes a noteworthy exception in the region where it grows (central and western Texas). On the other hand, the numerous species of pines, although producing abundant buoyant pollen, are only very rarely blamed for pollinosis. It may also be noted that the trees causing hay fever bear unisexual (imperfect) rather than perfect (hermaphrodite) flowers almost exclusively. There are only two exceptions worthy of mention—the elm and mesquite. Further than this, botanic classification is not useful for our purpose, since the trees under consideration include monoecious, dioecious, and polygamous types.

Various authors differ greatly as regards the order in which they list the trees according to their significance in relation to pollinosis. However, the important ones east of the Mississippi River may be taken to be the oak, maple, box elder, poplar, cottonwood, hickory, elm, ash, and sycamore. All of them, except the hickory and sycamore, also occur in the west, particularly on the Pacific coast, but the relative frequency with which they offend is, of course, different. In the south the list must take in also the pecan, which is closely related to the hickory, the hackberry, the mulberry, and the paper mulberry. Of secondary

importance nationally are the birch, beech, alder, walnut, hazelnut, linden, willow, pine, locust, and chestnut. Of local interest in various parts of the country (the first four only in portions of the southwest or far west) are the mountain and other cedars, mesquite, olive, acacia, tree of heaven, eucalyptus, and Australian pine. Finally, the shrub ligustrum and the bayberry bush, although not trees, may conveniently be included here. Each of these will be considered *serialim*.

Oak—Numerous species of oak occur in all parts of the United States and Canada. There are over two hundred in the central and eastern states alone. The oak is generally conceded to be the prime example of a tree causing pollinosis. Aside from the clinically unimportant evergreens the oaks are the most protuberant pollinating of the trees. In the east, the white oak (*Quercus alba*), red oak (*Q. rubra*), black oak (*Q. velutina*) and post oak (*Q. stellata*) are the most important. In the south, the live oak (*Q. virginica*) must also be considered, while the coast live oak (*Q. agrifolia*), scrub oak (*Q. dumosa*), Oregon oak (*Q. garriana*), tanbark oak (*Q. densiflora*), black oak (*Q. kelloggii*) and valley oak (*Q. lobata*) occur on the west coast. Numerous other types are known. Patients sensitive to one usually react to all. Pollination occurs chiefly in April and May, when the leaves are half grown, earlier in the south and on the Pacific coast. Individual species flower only for a fraction of the whole period, usually in succession.

Maple and Box Elder—These are both members of the genus *Acer*. Their wood is of great commercial value, and one species is the source of maple syrup and sugar. The maples are indigenous to the eastern third of North America and to the Pacific coast, but are cultivated elsewhere. The chief species are the silver or soft maple (*A. saccharinum*), red maple (*A. rubrum*), white or sugar maple (*A. saccharum*), and on the west coast, the Oregon maple (*A. macrophyllum*). The box elder (*A. negundo*) also known as the ash-leaved maple, achieves its greatest growth in the middle west. This genus pollinates rather earlier than the oak, some of its species are usually among the first to do so, but the box elder's season is generally in March or April. The various maples tend to flower at different times, giving rise to prolonged symptoms in a patient sensitive to them.

Poplar or Cottonwood—Poplars or cottonwoods—the names are used nearly interchangeably—are among the most widely distributed of trees. They are popularly planted for shade and ornamental purposes. The Carolina poplar or eastern cottonwood (*Populus deltoides*)—so named because of the triangular shape of its leaf—is probably the commonest of them, being represented in the west by the subspecies *P. sargentii*. Other widely ranging forms are the white poplar (*P. alba*), the quaking or trembling aspen (*P. tremuloides*), and the large-toothed aspen (*P. grandidentata*). In addition to the Sargent cottonwood, the Fremont cottonwood (*P. fremontii*), the black or large cotton-

wood (*P. trichocarpa*) the narrow leaved cottonwood (*P. angustifolia*) and the Arizona cottonwood (*P. arizonica*) are prominent in the west. The balsam poplar (*P. balsamifera*) occurs in the Mississippi valley and on the Pacific coast. The pollination of this genus is largely in April before the leaves appear. For some reason its pollen appears to cause less trouble in the central and eastern states than in the other regions where it occurs.

Hickory and Pecan—The hickory (*Carya* or *Hicoria*) is distinctively an American tree and is confined to the eastern portion of the United States. The commonest species are the mockernut (*Carya alba*) the pignut (*C. glabra* or *cordiformis*) and the shagbark or shellbark hickory (*C. ovata*). The pollen is shed in May and early June. The related pecan (*C. pecan*) of great commercial importance is widely planted throughout the south westward to Oklahoma and Texas. It pollinates profusely and is an important cause of hay fever where it occurs.

Elm—The most important of the trees bearing perfect (or hermaphrodite) flowers the elm occurs throughout the eastern United States and on the west coast. The spring flowering species which pollinate in March and April include the white elm (*Ulmus americana*) winged elm (*U. alata*) and slippery elm (*U. fulva*). In addition there are two fall flowering species the scrub elm (*U. crassifolia*) occurring in central and eastern Texas and portions of Oklahoma Arkansas Mississippi and Tennessee and the red elm (*U. serotina*) in Kentucky Tennessee northern Georgia Alabama and Mississippi. These pollinate from late August to the beginning of October and where they are present give rise to puzzling complications in ragweed hay fever.

Ash—Various species are distributed over most of the United States. The white ash (*Fraxinus americana*) which is widely employed as a shade and ornamental tree and the wood of which has great commercial value occurs throughout the east from the Atlantic coast to the plains. It flowers in April and May before the leaves appear. The red ash (*F. pennsylvanica*) and the black ash (*F. nigra*) are of lesser importance in the same region. Along the streams of the west coast the white ash is replaced by the Oregon ash (*F. oreogona*) which pollinates somewhat earlier. In New Mexico and Arizona the Arizona ash (*F. toumeyii*) and other species have some significance.

Sycamore—The sycamore also known as the plane or buttonwood tree is common in this country particularly in the eastern third and is a popular shade tree. It is characterized by the spontaneous shedding of its bark and the seed balls or 'buttons' that swing from its branches through the winter. The scientific name *Platanus* is derived from the broad shape of the leaf. The commonest type is the American sycamore (*P. occidentalis*) but the Oriental plane (*P. orientalis*) is cultivated in the western states and the California sycamore (*P. racemosa*) on the Pacific coast. Pollination occurs in the latter part of April and through May.

Hackberry—The hackberry related to the elm and resembling it in appearance is found throughout the United States except in Texas and the southwest but reaches its maximum growth in the Mississippi River

valley. Along with the pecan and mulberry it is of importance in relation to pollinosis only in the south. *Celtis occidentalis* is the most common species with the Mississippi hackberry (*C. mississippiensis*) chiefly notable in the southern states.

Mulberry—The mulberry one of the oldest cultivated trees occurs chiefly east of the Mississippi River from southern New York to Florida and as far west as Iowa and Texas. The red mulberry (*M. rubra*) is the most important with the white mulberry (*M. alba*) which is so extensively cultivated in the silkworm raising regions of the world of secondary significance. It flowers in May and early June as the leaves appear.

The paper mulberry (*Papirus papyrifera* or *Broussonetia papyrifera*) of a closely related genus is one of the most prolific pollinators known. The pollen is actually shot into the air as the anthers open and gives the tree the appearance of smoking. It occurs throughout the southeastern states most abundantly in the Carolinas Arkansas Georgia Alabama and Mississippi. Pollination takes place in the last week of April and through May. The osage orange or mock orange (*Toyodora pomifera* or *Maclura pomifera*) is also distantly related to the mulberry and is some times mentioned as causing pollinosis.

Birch—Various species of birch are found throughout the United States predominantly in the eastern half the white and yellow larches (*Betula alba* and *B. lutea* respectively) chiefly in the northern states and the yellow and the black birch (*B. lenta*) in the southern. The last named is the source of commercial oil of wintergreen. The red or river birch (*B. nigra*) tends to grow in moist soil. The paper or canoe larch (*B. papyrifera*) ranges over the northernmost states and into Canada. Crossed allergic reactions between the species are the rule. Birches pollinate early before the leaves appear. The related species ironwood or hornbeam (*Carpinus caroliniana*) and hop hornbeam (*Ostrya virginiana*) are of very limited importance in pollinosis.

Beech—The beech is a close relative of the oak both being members of the family *Fagaceae*. Like the oak it tends to hold its dead leaves well into the spring. The only important species is the American beech or beechnut (*Fagus grandifolia*) which occurs everywhere east of the Mississippi River and which sheds its pollen in May when the leaves are only partly grown.

Alder—The alder related to the birch has its maximum growth in the northeastern part of the country but is scattered from Florida to Texas as well. It has considerable importance in the northwestern coastal regions. The native alders are rarely more than shrubs that follow the watercourses. Chief species are the smooth alder (*Alnus incana*) and the hoary or speckled alder (*A. tenuifolia*). The thin leaved variety (*A. tenuifolia*) is found in the Pacific north west. They pollinate early before the leaves appear along with the first flowers of spring.

Walnut—The walnut is rather closely related to the hickory. The eastern varieties black walnut (*Juglans nigra*) and butternut (*J. cinerea*) are neither widely prevalent nor apparently very often the cause of pollinosis. However the native (or California) black walnut of the Sacramento valley (*J. californica*)

has been proved to be re-sponsible for many cases in that area. It is cultivated as a shade tree and as a stock on which to graft the English walnut. It pollinates in April and May.

Hazel—The hazel grows as a shrub over much of the country. The common hazel or American hazelnut (*Corylus americana*) and the beaked hazelnut (*C. rostrata*) are the outstanding examples. In addition, the California hazelnut (*C. californica*) appears on the west coast. The hazel blooms early, long before the leaves appear.

Linden—Attention has recently been directed to the linden or basswood (*Tilia americana*) as a cause of hay fever. Its range is from Maine to North Dakota and south to Georgia and Texas, and includes also southern Canada. Pollination occurs chiefly in May and June, but also as late as July in many places.

Willow—The willow (*Salix*) is characterized by the exceedingly wide range of its growth and its tendency to spontaneous hybridization. Its technical name reflects the fact that salicylic acid is abundant in its bark. It is partly wind and partly insect pollinated. This may partially account for its limited importance in pollinosis. The complex interrelationships between its various types make a discussion of its species point less. Different forms in various places may bloom at any time between March and June.

Pine—Although widely prevalent and producing abundant buoyant pollen, the pines (*Pinus*) only rarely cause pollinosis, apparently because of the low antigenicity of their pollen. However, cases of hay fever and asthma due to pine have been reported. The pollen is morphologically highly distinctive, consisting of a main body to each side of which is attached a wing or air bladder distended with a bubble of air. The so-called Australian pine is an unrelated species.

Locust—The black or honey locust (*Robinia pseudo-acacia*), so popular as a shade tree, has been found to be a cause of hay fever in occasional instances.

Chestnut—The chestnut (chiefly *Castanea dentata*, with *C. sativa* on the Pacific coast) lacks importance partly because the chestnut blight has greatly reduced its incidence, partly because it is to a considerable extent insect pollinated.

Cedar or Juniper—The so-called mountain or Mexican cedar (*Juniperus sabinoides* or *Sabina sabinoides*) is really a juniper, native to eastern and central Texas, extending southwestward, and found in New Mexico and Arizona. It is unique in that it pollinates in midwinter (middle of December to March). It has also been reported to do so when brought indoors as a Christmas tree. It is a major cause of hay fever in its region, and is the only plant flowering at that time. Other cedars of decidedly secondary importance are the Virginia or red cedar (*J. virginiana*) in Virginia, Tennessee, Arkansas, eastern Texas and Oklahoma, and the gulf states; the one-seeded juniper (*J. monosperma*) in the mountainous districts of New Mexico and Arizona; and the Utah "cedar" of the Rocky Mountain region.

Mesquite—The mesquite tree (*Prosopis*), which often appears merely as a low shrub, is native to western Texas, but occurs elsewhere. It has a relatively long pollination time (mid April to the end of July) and is

often covered with pollen several times between those dates. Several cases of hay fever due to its pollen have been reported. Honey or prairie mesquite (*P. glandulosa*) is the commonest type.

Olive—The pollen of the commercial olive tree (*Olea europaea*) is of some importance in California. Its season is May and early June. It is of interest to note that the olive is responsible for about a third of the spring hay fever cases in Spain.

Acacia—The acacia (*Acacia* or *Acaciella*) is the cause of some cases of pollinosis along the Pacific coast, chiefly in California. Its pollination season is rather variable, usually in the early spring, but it is said to be perennial in the San Francisco Bay area. The very closely related mimosa (*Albizia julibrissis*) should also be kept in mind.

Tree of Heaven—The tree of heaven (*Ailanthus glandulosa*), pollinating in June, probably can cause hay fever under certain conditions of exposure. It is planted as an ornamental growth in various parts of the eastern states.

Eucalyptus—The eucalyptus (*Eucalyptus*), also known as the blue gum or ironbark, is for all practical purposes limited in its growth to Florida and central and southern California. It is of secondary importance.

Australian Pine—The so-called Australian pine or Australian heefwood (*Casuarina*) pollinates throughout the winter in southern Florida, and its pollen has been proved to be a cause of hay fever.

Privet—The common privet hedge (*Ligustrum*), which is so widely planted, is not a tree but must be considered here. It will, if neglected, produce pollen of a low degree of "toxicity" from the end of May to the end of July. Pollination can be prevented by repeated trimming of the hedge. It has been suggested that it may exert its effects by means of the odor of the blossoms, rather than its pollen.

Bayberry Bush—Likewise not a tree, the bayberry (*Morrellia*) reaches its greatest growth in the southern states and should be borne in mind as a cause of sporadic cases of hay fever.

Grasses

The importance of the grasses may be appreciated from a few statistical facts. Over 1,200 species occur in the United States, sixty of them under intensive cultivation, and from thirty to sixty varieties in any single locality. About 75 per cent of the entire value of all farm crops is derived from members of the grass family. Although exceeded by a few other families in regard to total number of known species, grasses hold first place in regard to number of individuals, their ubiquity, range of habitat, and vigor and abundance of growth. Moreover, they constitute the chief form of vegetable food for man and domestic animals. There are, of course, other uses,

since they are the source of sugar, alcohol, beverages, and straw

The grass family may be divided into the cereal grains (including wheat, rice, corn, oats, rye, and barley) and the meadow (or hay) and pasture grasses depending on the uses to which they are put. Certain species must be placed in both the latter categories. They should be distinguished from the botanically allied rushes (*Juncaceae*) and sedges (*Cyperaceae*), which, by reason of the density of the outer coat (extine) of their pollens, are harmless in hay fever.

From the standpoint of pollinosis, the grasses, in addition to their untold numbers, produce abundant wind borne pollen. In this connection, it may be noted that the pollens of the various species are morphologically indistinguishable, differing only in size. When dry, the grains are smooth, either collapsed or presenting several small depressions. In an aqueous medium they become sphenical or nearly so, with a slightly granular surface. Because of their high starch content, they all stain deeply with iodine. It is of interest to recall that the pioneer experiments of Blackley were performed with grass pollen.

While the weeds exceed grasses in the amount of pollen they produce, the number of hay fever victims for which they are responsible, the severity of the symptoms they cause, and the length of their season in this country, grass pollinosis is the outstanding type else where throughout the world.

Grass pollen is responsible for practically all the hay fever occurring in the late spring and early summer (May to July in most sections of the United States). Although, in most places, the pollination of some types often begins sooner and ends later, it is not generally of sufficient degree to have any clinical significance outside of the period stated, except under unusual circumstances. However, in certain years, in such widely separated localities as New York City, Ames, Iowa, and Charlotte, N. C., as many grass pollen grains have been reported to be found on exposed slides during August or September as during June and July. It should also be noted that in the gulf region, in irrigated areas of Texas and Arizona, as well as in California and elsewhere, grasses may continue to pollinate

throughout the year. It will be seen from the discussion in the preceding section that the seasons of the late-blooming trees such as birch, sycamore, and walnut, and to a lesser extent oak, overlap the beginning of the grass season. Moreover, in most places English plantain pollinates at the same time as the grasses, although continuing much later, into the fall. Other possibilities of confusion arise because of the pollens of such entomophilous plants as dandelion, daisy, clover, and alfalfa, usually as a result of intimate contact and in agricultural workers. However, the generalization that grasses cause summer hay fever in the vast majority of cases is undoubtedly true.

Hay fever patients in the eastern United States frequently have symptoms in the interim period from the last week of July until mid August, during which sufferers sensitive to both grass and ragweed pollen should be symptom free. Chobot and Dundy⁹⁵⁷ pointed out that manifestations during this period are often due to pollens of marsh elder (*Iva frutescens*), cultivated corn (*Zea mays*), wild rice (*Zizania palustris*), and cocklebur (*Xanthium*), as well as to the spores of the fungus *Alternaria*. Concomitant sensitiveness to house dust, feathers, and animal danders must also be considered.

With regard to the comparative incidence of grass and ragweed hay fever, we may cite the statistics of French and Halpin.⁹⁵⁸ Of a total of 1,269 soldiers classified as cases of uncomplicated seasonal hay fever, approximately one half were of ragweed origin, one eighth of the grass type, and three eighths had both grass and ragweed sensitivity.

The apparent complexity of the problem of grass pollinosis is greatly diminished by the fact that relatively few of the hundreds of known species are sufficiently prevalent or shed pollen of sufficient allergenicity to cause many cases. Parenthetically the state of California is a partial exception to this statement, since at least two dozen grasses are stated to have some importance in pollinosis there. Moreover, in the opinion of some authorities, the existence of a cross reactivity between various types simplifies the therapeutic approach.

⁹⁵⁷ CHOBOT, R. and DUNDY, H. D. *J. Allergy* 15: 187, 1944.

⁹⁵⁸ FRENCH, S. W. and HALPIN, L. J. *Ann. Allergy* 1: 1, 1943.

With very few exceptions, the important grasses in this connection are those that are intensively cultivated for forage, or that have escaped cultivation and grow wild

Five species of grasses far exceed all others as causing pollinosis: timothy, June or Kentucky blue grass, orchard grass, reedtop, and Bermuda grass, the last-named only in the southern

to discuss the allied plants, cat tail, clover and alfalfa.

Timothy (Fig. 90)—*Timothy* (*Phleum pratense*), also known as Herd's grass, is the most extensively cultivated hay grass in America far exceeding all the others combined and may be taken as the "type" for hay grasses. It occurs throughout the northern United States (as far south as Tennessee) and in



FIG. 90. TIMOTHY (*Phleum pratense*)

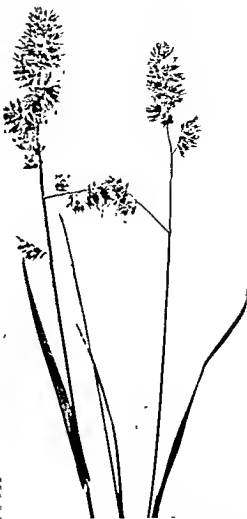


FIG. 91. ORCHARD GRASS (*Dactylis glomerata*)

states. Of secondary importance are sweet vernal grass, the ray or rye grasses, Johnson grass, fescue, Canada and other blue grasses, wheat or quack grass, velvet grass, and canary grass. Of minor significance are brome grass, panic grass, crab grass, beard or broom grasses, bent grass, foxtail grass, grama grass, paspalum, salt grass, and finally the cereals and related wild grasses. It is also necessary

Canada, but is particularly abundant in the humid portions of the northeastern part of the country. It is rare in the gulf states and the southwest (except at high altitudes), but occurs on the Pacific coast. Originally introduced from Europe in the first half of the eighteenth century, it soon escaped cultivation and now grows "wild as a weed" in waste places and neglected fields. Its common names derive from those of a New England farmer, Herd, and Timothy Hansen of Maryland, respectively, both of whom were instrumental in introducing it. A related species native to

American mountain timothy (*P. alpinum*) is of little consequence. Timothy is a perennial in that only the stems die down to the roots each winter and new ones being formed from buds at the base of the shoots the next year. Its pollination is chiefly in June and July, usually placing it along with redtop among the last to start in its habit.

As stated its pollination is through June from May to July.

Orchard Grass (FIG 91) —As the name implies this grass grows well in shaded places as in orchards. It is a tall perennial used as both a pasture and meadow (or hay) grass the latter in sections where timothy does not grow. It is present in nearly every state



FIG 92 REDTOP (*Agrostis alba*)

June Grass —This is America's most important pasture grass and at the same time a favorite lawn grass. Like timothy it is a perennial and was introduced from the Old World where however it is not of much importance. June grass (*Poa pratensis*) is also known as blue grass or Kentucky blue grass—the first because of the time of its flowering the last because it produces the effect of the famous blue pastures of that state. Its distribution is much like that of timothy since it is present in every part of the United States though rare in the Gulf region. It flourishes in the northeastern, north central and Pacific northwest areas. It requires a cool moist climate and soil rich in lime. When uncut it will reach a height of 3 feet

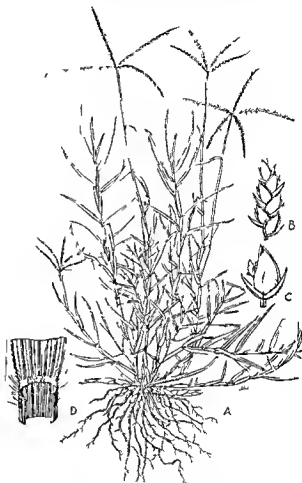


FIG 93 BERMUDA GRASS (*Cynodon dactylon*)

extending farther south than timothy or June grass but is most abundant east of the Mississippi and north of Alabama and Georgia. It is said to be the chief offending grass in Baltimore. Orchard grass (*Dactylis glomerata*) is also known as cocksfoot, dew grass and hand grass. It flowers from May to July, its pollen joining with that of June grass to form an early grass peak while timothy and redtop create a later one.

Redtop (FIG 92) —This is a perennial grass useful for both hay and pasturage. Redtop (*Agrostis alba* formerly *A. palustris*) is so named because its blooming spikelets are of a reddish or purplish red color. It is also known as whitetop, summer dew grass and white marsh or creeping bent. It has about the same dis-

tribution as orchard grass, but, unlike the latter, prefers moist meadows and pastures, and soil poor in lime. It is more abundant in the northern part of the eastern gulf states and in the humid regions of the Pacific northwest. It is absent from the drier regions of the extreme south. Its pollination occurs in June and July.

Bermuda Grass (FIG 93)—While the four species described above are predominant in the northern two-thirds of the United States, Bermuda grass is beyond doubt the commonest in the southern states. There is an overlapping zone extending westward from Virginia and North Carolina in which all of them may grow. The intense suffering caused by Bermuda grass has given rise in some areas to the local name of "devil grass." Other designations by which it is known include scutch grass, wire grass, Bahama grass, and many others. Supposedly native to Bengal India it does not occur in Bermuda. Bermuda grass (*Cynodon dactylon* or *Cephalis dactylon*) is prevalent throughout the south from Maryland to California. While it does occur much farther north (extending only the northernmost tier of states), it is not sufficiently abundant to require consideration. Its unique value as pastureage in the region of its growth lies in its ability to withstand heat and long periods of drought. Its range and acreage are gradually being extended. The season of its pollination is quite variable, and it will bloom in the winter and even perennially under favorable conditions in the gulf states and the irrigated regions of Texas and Arizona. In general, however, it has a long season, from April to November, although pollination ceases when the weather is very hot and dry. It does not rival the northern grasses in the quantity of pollen produced.

Sweet Vernal Grass (FIG 94)—Probably the most important of the secondary grasses, sweet vernal (*Inthoanthum odoratum*) is widely if not abundantly distributed over much of the country east of the Mississippi River, as well as in Louisiana and on the Pacific coast. However, its ability to resist cold and drought, and to grow in even poor soil, accounts for its reaching its greatest concentration in the New England and middle Atlantic states. Here, it is often the first of the grasses to pollinate, starting early in May.

Kay or Rye Grasses—First introduced from England, rye grass still persists, largely in the states comprising the original thirteen colonies, and to a lesser extent in the other states. English or perennial rye grass (*Lolium perenne*) is also known as darnel or red ray. This and the rather similar Italian rye grass (*L. multiflorum*) occur on the Pacific coast. The latter is the chief meadow grass in Europe. As a cause of pollinosis, the rye grasses have their chief importance in California. Their pollinating season extends from May to July, and into August.

Johnson Grass.—Rarely cultivated now, this grass, which is a comparatively recent importation from Turkey, has become a troublesome weed, difficult to eradicate. Interestingly, it can, under certain conditions, contain enough hydrocyanic acid to be poisonous to livestock. Johnson grass (*Holcus halepensis*, formerly known as *Andropogon halepensis* and *Sorghum halepense*) is also called Means grass, millet, maiden

cane and Cuba grass. It occurs chiefly in the south, reaching its greatest importance in Oklahoma, Texas, and southern Arizona. While its pollen is rather scant and heavy, the local abundance of the plant partially compensates for this. A subvariety, Sudan grass (*Holcus sudanensis*) has its maximum growth in California. Both it and another subvariety, sorghum (*H. sorghum*) or millo maize, are extensively cultivated throughout the arid and semi-arid regions of the country. The pollination of Johnson grass, and in most places of its relatives, continues from May to November.

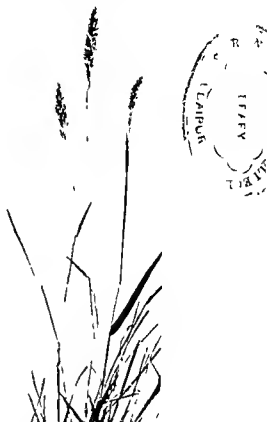


FIG 94 SWEET VERNAL GRASS
(*Inthoanthum odoratum*)

Fescue—Fescue is indigenous to all of Europe, second only to *Lolium* as a meadow grass, but is of little agricultural importance in this country. The chief example is meadow fescue (*Festuca elatior*), which occurs in restricted areas, as in western Missouri and eastern Kansas, and in a scattered way elsewhere, including the west coast. Its pollination centers about June and July.

Canada Blue and Other Blue Grasses—Far less common than their widespread relative, June grass, the other blue grasses still have considerable importance. Canada blue grass or wire grass (*Poa compressa*) actually has a greenish-blue coloration, and blooms from June to August. Annual blue grass (*P. annua*), also called low spear grass, dwarf meadow

grass and walk grass is a nuisance in lawns and is characterized by an unusually prolonged pollination which under favorable conditions can take place in any month of the year. In most places where it occurs it is usually among the first of the grasses to pollinate but does so scantily. Both species are present practically throughout the United States but somewhat more abundantly in the north central states the first named also in the northeastern states the last named particularly in California.

areas mentioned it pollinates from April to August. It does occur elsewhere but is not of much consequence.

Canary Grass—Canary grass (*Phalaris canariensis*) receives its name from the fact that its seed is used as a bird food. It was imported from the western Mediterranean region and appears in waste places in the south but flourishes particularly in California. Other species of *Phalaris* such as Mediterranean or small canary grass (*P. minor*) and gnawed canary grass (*P. paradoxa*) are far less important.



FIG 95 CRAB GRASS (*Syntherisma sanguinale*)

Quack or Wheat Grass—A rather large number of species of this grass grow in all parts of the country except the south. They are especially characteristic of the Rocky Mountain states. The chief of them *Agropyron repens* has gained accidental importance as a forage grass in many places and is a difficult weed to eradicate. Its numerous common names include wheat or quack grass, couch grass, blue stem, quitch grass, witch grass and bunch grass. Its scanty pollination is usually in June and July.

Velvet Grass—This grass is so named because of the hairiness of its leaves. Velvet grass (*Natholcus lanatus*) is common chiefly along the Pacific coast south from British Columbia, least so in southern California. It is the most important hay fever excitant in the coastal regions of Washington and Oregon. In the

Brome Grass—Brome grass occurs predominantly in the western portion of the United States where it plays some part in pollinosis. While present elsewhere it is not very abundant. Leading varieties are soft cheat or chess (*Bromus mollis* or *hordeaceus*), California brome (*B. carinatus*), smooth brome (*B. inermis*), rescue grass or southern chess (*B. unioloides*) and downy brome grass (*B. tectorum*). Broncho grass (*B. villosus*) has received some attention in California. The pollination of the brome grasses occurs somewhat variably generally from May to July.

Panic and Crab Grasses (FIG 95)—The genus *Panicum* is represented by a great many species in most parts of the country but occupies a rather minor position in relation to pollinosis. It is known as panic grass, witch grass and millet. Various types flower

between June and August. Related species include crab or finger grass (*Digitaria* or *Syntherisma sanguinalis*), pollinating in July and August or later, and barnyard grass (*Echinochloa crus galli*), which has a variable and rather long season. Both are widely distributed in a scattered way. St. Augustine or short grass (*Stenotaphrum secundatum*) occurs in the southern states and flowers almost continuously. It may be of minor importance in the Gulf region and in Florida.

Beard or Broom Grass—Several species of *Andropogon*, which is related to Johnson grass, have been reported as minor offenders from various parts of the United States, chiefly the south and midwest. Popular names include blue stem, beard grass, broom grass, and milo maize. Most commonly mentioned are *A. furcatus*, *A. scoparius*, and *A. virginicus*. Its pollination occurs from July to September in the north central states and as late as October or November in such places as Alabama, Florida, and Louisiana.

Bent Grass—Of the same genus as reedtop, the white-top (*Agrostis exarata*), maritime bent (*A. maritima*), and water bent grass (*A. verticillata*), are of importance only on the Pacific coast. Their pollination largely coincides with that of reedtop.

Foxtail Grass—Significant quantities of this grass have been reported from the Pacific northwest and in Louisiana. The two chief representatives are yellow foxtail or pigeon grass (*Setochloa glauca*) and green foxtail (*C. viridis*). Like the panic and crab grasses, they pollinate in the summer.

Grama Grass—Grama or gama grass (*Bouteloua*) appears to have its greatest importance in the southwest, but has also been reported from Colorado and Minnesota. It flowers in July and August, but commences earlier in Arizona.

Paspalum—Paspalum or bull grass resembles Bermuda grass in appearance and has roughly the same distribution. The most common type is knot grass or joint grass (*Paspalum distichum*), which pollinates from July to September. Dallas grass (*P. dilatatum*) is said to be one of the most abundant grasses in the vicinity of New Orleans.

Salt Grass—Salt grass or marsh spate (*Distichlis spicata*) is fairly prominent on the Pacific coast, where some authors have found it to be a frequent "skin reactor." It extends as far east as central Colorado but also occurs in the salt marshes of the east coast. Its pollination takes place from April to July or early August.

Cereal Grains and Related Wild Grasses—The cereals as a group are of decidedly minor importance in hay fever, since several of them (wheat, oats, barley, and rice) are self-pollinated and all have large, rather heavy pollen grains that are not readily wind-borne. However, the large areas given over to cultivation of them, and the close contact farm workers and dwellers have with them, make it undesirable that they be completely overlooked, especially as regards corn (*Zea mays*). * Rye (*Secale cereale*), which is more intensively

cultivated in Europe, has a correspondingly greater importance there (Fig. 96).

In this connection, the wild "cousins" of the cereal grains may be mentioned. Wild barley, also known as squirrel-tail and foxtail (*Hordeum jubatum*), and wall barley or farmer's foxtail barley (*H. murinum*) are prominent in the west, particularly in California. Little barley (*H. pusillum*) occurs in the Gulf states



FIG 96. RYE (*Secale cereale*)

Wild oat, both common (*Avena fatua*) and slender (*A. barbata*), attains its greatest growth in California, but is found elsewhere. Finally, wild rye has a broader distribution, with slender or alkali wild rye (*Elymus triticoides*), western (*E. glaucus*) and giant wild rye (*E. condensatus*) occurring in the west, and Virginia wild rye or terrell (*E. virginicus*) in the east.

Cat-tail—Although not a grass, cat tail (*Typha latifolia* and *T. angustifolia*) may conveniently be considered here. It sheds abundant pollen that is unique in that it shows persisting tetrads (four pollen grains

* In cities, grocers and cooks have been known to be affected as a result of handling pollen-covered husks.

adhering to one another by protoplasmic filaments) It is a marsh plant and has been reported from widely separated areas It is an offender only in rare cases Its pollination is mostly in June, earlier on the gulf and Pacific coasts

Clover and Alfalfa—Clover and the related alfalfa of the family Leguminosae are likewise not grasses but are of course, extensively cultivated Although normally insect pollinated, dry clover and alfalfa in the form of hay when subjected to pitching by farm workers give rise to what are under those circumstances atmospheric pollens Such dissemination of pollen is, of course independent of the actual pollinating seasons of these plants, which are usually between June and September Chief representatives are red clover (*Trifolium pratense*), sweet white clover or white melilot (*Melilotus alba*), and cultivated alfalfa (*Medicago sativa*)

Weeds

It has long been customary to classify the plants whose pollens cause hay fever into types as trees, grasses, and weeds However, it has already been noted that many of the important grasses have escaped cultivation and are in reality agricultural nuisances Moreover, some of the plants included here are actually cultivated in gardens, in flower plots, and commercially In general, however, most of the species in this category, and certainly the outstanding representatives, are true weeds, that is, valueless in themselves and unsightly or troublesome in agriculture They are characterized by a remarkable ability to propagate, even under adverse conditions This accounts for their prevalence in neglected fields, along roadways and railroad right of ways, in vacant lots in metropolitan areas, and in waste places of all sorts, as well as in cultivated ground, particularly after crops are harvested Moreover, their seeds are unusually hardy, and may be distributed by a wide variety of means, namely by the wind, in grain, grass, or clover seeds, by farm implements, in the wool, hair, or feathers of livestock, wild animals, poultry, or birds, in manure used for fertilizer, in or on commercial shipments, especially in packing material, etc Furthermore, they are difficult to eradicate, even when a determined effort is made Hence they constantly tend, except as checked by unsuitable soil or unfavorable meteorologic conditions, to increase their range

This profusion of numbers, plus the nearly unbelievable abundance of pollen that single

stands of many species are able to produce over considerable periods of time accounts for the huge quantity of pollen grains discharged into the air And the buoyancy of the pollen, which permits it to be wind-borne for many miles, along with its "toxicity" or antigenicity, explains why weed hay fever is so severe and so prolonged in this country In this connection, it is interesting to note that in Europe and elsewhere in the world, where such weeds either do not grow at all or do not occur in abundance weed hay fever is absent It is, therefore, a uniquely American phenomenon

Hay fever producing weeds may be annual, biennial, or perennial as regards duration of life The prominent ones, however, are mostly annuals Weeds may be wind-pollinated (anemophilous) or insect pollinated (entomophilous) While obviously the former type is the more important, the latter, for reasons indicated elsewhere, should not be entirely disregarded To cite only a few examples, the conditions of exposure are vastly different from what one would be led to expect from the results of pollen slides exposed on a window ledge in a city, or even from a local botanic survey, under the actual circumstances of automobile or train riding, of agricultural work, golfing, hunting, and picknicking, and of playing in the fields, in the case of children

As a broad generalization, the hay fever season due to weed pollens lasts, in most parts of the United States, from mid August until frost occurs There are numerous exceptions particularly in the southwest, on the Pacific coast, in the Pacific northwest, and in Florida, where pollination tends to begin earlier Moreover, plantain, which is really a weed, pollinates at the same time with the grasses, although continuing later It should also be noted that in the south and in California, Bermuda grass may continue to pollinate well into the weed season

Unquestionably, the ragweeds are the most important plants from the standpoint of pollinosis, and are said to account for 75 per cent of the hay fever in the eastern half of the United States At the same time, the statement is made that in only a very small portion of the cases, even in the worst part of the ragweed belt, is pollen hypersensitiveness restricted exclusively to ragweed Hence the

desirability of recognizing and taking into consideration the others of the known offenders West of the ninety-fifth meridian of longitude (about at the eastern boundary of Kansas), the most important pollens are those of the sages, Russian thistle, burning bush (Mexican firebush), western water hemp, and the amaranths.

Our discussion will be facilitated by considering the weeds according to their botanic grouping. This will be done roughly in the order of relative importance of the groups, as follows:

The pigweed family (*Amaranthaceae*), including the amaranths or pigweeds, and western water hemp;

The goosefoot family (*Chenopodiaceae*), including lamb's-quarters, Russian thistle, sea blite, burning bush, orache or shad scale, winter fat, and greasewood,

The plantain family (*Plantaginaceae*), comprising the plantains,

The buckwheat family (*Polygonaceae*), including sorrel and dock,

The hemp family (*Cannabinaceae*), including hemp and hop.



FIG. 97. A, GIANT RAGWEED (*Ambrosia trifida*) B, DWARF RAGWEED (*A. elatior*)

The composite family to which belong:

The ragweed group (*Ambrosiaceae*), including the ragweeds, false ragweeds, marsh elders, and cockleburs,

Other *Compositae*, including the wormwoods, sagebrushes, mugworts, golden-rods, sunflowers, asters, dahlias, daisies, and dandelion.

The Composite Family

The Ragweed Group (tribe *Ambrosieae*)—Of the eight known genera in this tribe, only four need concern us here. They are the ragweeds, the false ragweeds, the marsh elders, and the cockleburs. There is undoubtedly a considerable antigenic interrelationship between them. Moreover, their pollens are morphologically nearly identical, all of them being small, dry, buoyant, and spherical or nearly so. With the exception of those of the cockleburs, which are smooth-

walled and somewhat larger all of them are covered with short pointed or slightly rounded spines

(1) *Ragweeds* (FIG 97) As mentioned above the ragweeds are beyond question the chief hay fever offenders in the east and south Common dwarf or short ragweed (*Ambrosia deltoidea* or *A. artemisiifolia*) and giant or tall ragweed (*A. trifida*) are annuals sharing approximately the same distribution through the entire east* except upper New England and the coastal areas of North and South Carolina and Georgia as well as portions of Florida West of Kansas and western Texas they show a sharp decrease in abundance their places being taken by western ragweed and marsh elder but they do range to the foothills of the Rocky Mountains and beyond Giant ragweed extends farther than the dwarf variety into Colorado and New Mexico They are usually absent at elevations above 5 000 feet The northern limit of their growth is beyond the Great Lakes and the St Lawrence River in the prairies of Manitoba and Saskatchewan They also occur in Mexico and Cuba

The familiar dwarf ragweed generally ranges from 1 to 3 feet in height (FIG 98) and grows profusely in waste places at roadsides in vacant lots and neglected fields The giant ragweed which differs from the dwarf chiefly in size of plant and in shape of leaf often reaches 15 feet or more in height and requires moist soil for its growth In all places in which they occur the dwarf exceeds the giant ragweed in abundance (particularly in New England) except in the gulf region notably around New Orleans in local areas of the Missouri and the Mississippi River valleys and at points around Lake Erie However the size of the individual plants and the huge quantities of pollen that one giant ragweed can produce tend to compensate for this difference

Pollination lasts from mid August till late September or early October except in the gulf states where it starts somewhat later (one to three weeks) and continues into November In certain regions of Florida and Louisiana the period of anthesis may commence in May In most places the giant type commences its pollination slightly earlier than the dwarf

Four other species of the same genus are of considerable importance in their respective areas However since they occur in the less thickly populated regions and have less of a tendency to grow in cities and towns their pollens are correspondingly less likely to reach human mucous membranes Western ragweed (*A. psilostachya*) is a perennial that otherwise closely resembles its eastern (dwarf) relative and is found west of the Mississippi River most abundantly in western Oklahoma the western and southern portions of Texas and the coastal regions of California Variants are *A. coronopifolia* of the Great Plains area and *A. californica* of southern California In the southern part of its range it may bloom as early as May continuing until late fall but principally in September and October It is the principal ragweed west of the Rocky Mountains but is still far exceeded in impor-

tance in most areas by other weeds The (Texas) great ragweed or giant western ragweed (*A. aptera*) has a much more limited range confined for all practical purposes to Texas and the southwestern states although it does occur in Louisiana and Mississippi Both species pollinate in most localities from July to October or later Southern or lance leaved ragweed (*A. biidentata*) is less important occurring locally in the lower Mississippi valley from southern Illinois to northern Louisiana in parts of Texas and in the dry soil of the Ozark region Pollination is usually complete between August and mid September Tia Juana ragweed (*A. parvifolia*) is a low inconspicuous weed found in Lower California where it may be a local factor

(2) *False ragweeds* Botanists have placed false ragweed (*Franseria* or *Gastriaria*) in a different genus from ragweed despite many similarities It is stated that the pollens of false ragweed intersect on skin testing with those of true ragweed The *franseria* occupies a position of considerable significance in the west probably second only to the *artemisia* and *ivas* Slender false ragweed (*F. tenuifolia*) is an annual occurring from Kansas southward to Texas and westward to the coast but chiefly in Arizona and southern California It pollinates from May to November but more abundantly in the latter portion of this period Bur ragweed or false (western) ragweed (*F. acanthocarpa*) is an annual or biennial common to the plains sandy valleys and mountain ranges from Missouri westward, and flowering in the fall

Some species are perennials and three of them pollinate in the spring (in March and April) and to a lesser extent in (June) rabbit bush canon ragweed or erroneously named sagebrush (*F. deltoidea*) bush sandbur (*F. dumosa*) also called burro weed or desert bur sage, and Sonora bur sage (*F. ambrosioides*) They are important only in the southwestern states Also present in this region as well as in California but less abundant are common beach sandbur (*F. bipinnatifida*) and Chamisso's sandbur (*F. chamissonis*) They grow on the seashore or on sandy dunes and pollinate through both grass and weed seasons (May to September or October)

(3) *Marsh elder* (FIG 99) This group with a multiplicity of common names has its greatest significance in the midwest and in the Rocky Mountain region The most important is known variously as burned marsh elder high marsh elder careless weed prairie ragweed high water shrub horseweed or giant poverty weed (*C. xanthifolia*) An annual growing 2 to 6 feet high it is found throughout the northeastern United States to the Rocky Mountains particularly abundantly in the wheat belt where it is an important factor in hay fever Some authorities place this weed in a separate genus with the scientific name of *Cyclochaena xanthifolia* and consider as true marsh elders only those species named below True or rough marsh elder (*C. alata*) extends from the Mississippi valley to western Kansas and occurs less profusely in the southwestern states In some localities as in the northeastern part of Louisiana it is even more important in hay fever than the ragweeds Less extensive in its

* The center of the ragweed belt where the fall of pollen is heaviest lies in Indiana

distribution, the poverty weed small poverty-weed small flowered marsh elder or western elder (*I. arifolia*) is a perennial occurring in the mountain states and the southern half of California. One species of

from the middle Atlantic and southern states. All the *Iva* pollinate in August and September or October poverty weed starting somewhat earlier (even in April or May in some places). Their pollen grains are much



FIG 98 STAND OF DWARF RAGWEED (*Ambrosia elatior*)

common marsh elder, also called high water shrub (*I. oraria*) is confined to the east, where it grows in tidal marshes and extends up the rivers. A variant, scrubby marsh elder (*I. frutescens*) has been reported

like those of ragweeds, though the spines are somewhat less prominent.

(4) Cocklebur (FIG 100) Although a very common weed, cocklebur is of less importance than the weeds

above described probably because its pollen grains are rather large and most of its species produce only scant amounts. *Xanthium commune* and the Pennsylvania cocklebur or clotbur (*X. pennsylvanicum* or *canadense*) are found in waste places roadsides and recently cultivated fields in every state. Another species the great clotbur (*X. speciosum*) occurring in the midwestern southwestern and mountain states pollinates somewhat more abundantly. Spiny or thorny clotbur or clotweed (*X. spinosum*) is of minor significance everywhere except in California where it is more prevalent. The cockleburs pollinate chiefly in



FIG 99 MARSH ELDER (*Iva xanthifolia*)

August and September the last named continuing somewhat later. Their pollens interreact with each other and largely with those of the ragweeds.

Other Compositae.—The composite family is the largest of the plant families comprising hundreds of genera and over ten thousand species and is considered to represent the highest plane of evolutionary development. The ragweeds are included as a tribe in this family but for reasons of simplicity we have elected to discuss them separately. Most of the cultivated garden flowers and the most colorful of the wild flowers belong to this family. From the standpoint of pollinosis however these rank far below the outstanding genus *Artemisia*.

(1) *Artemisia*. This is a very large genus with over one hundred species at least twenty seven of which are mentioned in the literature as causing hay fever. Need less to say not all of them are major offenders. This group includes the sages and sagebrushes wormwoods sageworts and mugworts. Their wide distribution

their capacity to thrive under conditions unsuited to the majority of plants and the lightness of their pollen make them the most important group in relation to hay fever in the Pacific and Rocky Mountain states. The pollen grains of all the artemisias are three lobed and are all smooth with the exception of those of biennial wormwoods which are slightly spiculated. Unfortunately not only are the common names confused but there are differences of opinion as to the botanic relationships of various forms.

The most important is probably the common sagebrush (*A. tridentata* formerly *A. tridentata*) which is the most abundant and most widely distributed plant in all of western North America extending from New Mexico and southern California across the Great Basin into Washington and Montana. It covers literally thousands of square miles almost to the exclusion of all other plants in parts of Nevada Utah and Colorado. Typically a low shrub it can attain a height of 12 feet or more and shed huge quantities of pollen. Pasture sage (*A. frigida*) also known as carpet or prairie sage and mountain sage is a low herb characteristic of the mixed prairie growth and very abundant in the Rocky Mountain region covering the ground in parts of Utah and Colorado and being especially profuse in and around Denver. It is slightly more common in the northern part of the Great Plains than the southern. These two artemisias are important causes of hay fever west of the Mississippi River except in the lower Mississippi valley. They pollinate from July to October or November.

Of the remaining sages two are common in the Pacific coast states coast or coastal sagebrush hill sage California sagebrush or California old man (*A. californica*) and somewhat less so field sagewort or seashore mugwort (*A. pycnocephala*). Hoary sage (*A. cana*) has been reported from the Dakotas and California prairie or gray sage (*A. Wrightii*) from Utah and southernwood (*A. abrotanum*) from Minnesota and the eastern parts of the Dakotas.

Several species of *Artemisia* can be considered as closely related varieties or subspecies of *A. vulgaris* and are all known as wormwoods. Common sagewort or mugwort (*A. vulgaris*) (FIG 101) a native of Europe and Asia is found widely scattered from Newfoundland and Georgia westward to Alabama Wisconsin and western Canada. It is of limited importance in hay fever and pollinates from July to October. Mugwort California mugwort sagewort prairie or white sage (*A. vulgaris heterophylla*) is the most abundant of the subgroups particularly through the valleys of California and eastward to the Great Plains. This or the closely related subspecies *A. gnaphalodes* which is not recognized by some authorities actually extends eastward in a scattered way as far as New Hampshire and Massachusetts though not in any significant quantity. The pollination time of mugwort is from July to November. Biennial wormwood (*A. biennis*) an annual or biennial pollinating at the same time is more widely distributed occurring in open places—especially ditch banks and neglected yards—throughout the land except in the southeast although most abundantly in the valley of the Mississippi River and its

tributaries. Also known as prairie sage or white sage brush, but possibly better referred to as dark-leaved mugwort, *A. ludoviciana* is widely found in western North America. Dragon sagewort (*A. dracunculus* or *A. dracunculoides*), also called Indian hair tonic taragon, green sagebrush, and "smooth ragweed," is common on the plains and in the mountains westward from Illinois, but absent from the desert prairies. These last two pollinate in August and September

found almost throughout North America except in the desert regions and are of some importance in pollinosis. Field sagewort (*A. camporum* or *A. campestris pacifica*) is the common form in the western states, from South Dakota and western Nebraska to New Mexico, Arizona, and Oregon. An indication of overgrazing it is unpalatable to stock, sheds its pollen in the late summer and fall, and is a cause of hay fever in the Rocky Mountain region. Tall wormwood (*A.*



FIG. 100 COCKLEBUR (*Xanthum*)

Less important wormwoods are absinth (*A. absinthium*), annual or sweet wormwood (*A. annua*), and tall or wild wormwood (*A. canadensis*), which have been reported, in small quantities to be sure, as far east as Yonkers, N. Y., Toledo, Ohio, and Chicago respectively. Green sage or Canada wormwood (*A. canadensis*) is found in Minnesota and the Dakotas.

Four species are regarded as varieties of field sagewort (*A. campestris*), being biennial or perennial herbs

canadensis or *A. campestris canadensis*) occurs on sandy shores and dunes of the eastern and central states, especially in the upper Mississippi valley, and pollinates profusely in August. It is prevalent in and around Minneapolis and St. Paul. Silvery wormwood or sand sagebrush (*A. pycnostachya*) extends from Nebraska and Wyoming to Nevada and Texas, and may cause hay fever in the latter portion of the summer. Budbrush, bud-sage, or spiny sagebrush (*A. spinescens*) is

found on arid planes and slopes from Montana and Colorado to New Mexico eastern California eastern Oregon and Idaho and flowers from March to June

(2) *Goldenrod* (Fig 102) The much maligned goldenrod (*Solidago*) is contrary to the general lay belief not an extremely important plant in pollinosis. The confusion has arisen from its flowering at the height of the fall hay fever season when it is so striking in

(3) *Other Compositae* Although they do not produce positive skin tests as commonly very much the same evaluation could be applied to the following flowers of which the first four of course are wild sunflower (*Helianthus annuus*) dandelion (*Taraxacum officinale* or *T. taraxacum*) daisy (both yellow Red



FIG 101 COMMON MUGWORT (*Artemisia vulgaris*)

appearance in waste places. Although largely insect pollinated its pollen grains can be identified on slides exposed even in the center of large cities and toward the end of the season when ragweed pollen becomes scarce or in dry windy weather in not insignificant numbers. Moreover exposure is rather intimate in the case of persons working or playing in or near fields covered with this plant. Sometimes goldenrod is brought indoors for decorative purposes. A large proportion (said to be 30 per cent) of ragweed cases react to tests with its pollen. It is found throughout the United States more commonly in the east than in the west.



FIG 102 GOLDENROD (*Solidago*)

beetle hirta and oxeye *Chrysanthemum leucanthemum*) dog fennel (*Eupatorium capillifolium*) aster (Aster) dahlia (*Dahlia variabilis*) cosmos (*Cosmos bipinnatus*) and many other cultivated plants. They can be responsible for sporadic cases of pollinosis in amateur and professional gardeners and in others. Other wild or in gardens they can be found in all parts of the country dandelion being particularly prevalent in portions of the Pacific northwest. Dandelion and daisy pol

linated during the grass season, the garden flowers in the late summer or fall. Positive dandelion reactions are stated to be usually associated with positive ragweed reactions. Hence, when a ragweed allergic experiences symptoms before his usual season, this weed should be suspected.



FIG 103 PIGWEED OR AMARANTH (*Amaranthus*)

The Pigweed Family (Amaranthaceae)—The members of this family morphologically resemble those of the goosefoot family, which will be considered next. Both belong to the order *Chenopodiales*. The pollens of both are microscopically indistinguishable, all being round and multiple-dimpled, like a golf ball. Moreover, interactions on skin testing are the rule. Of the two score genera of *Amaranthaceae* that are recognized, only two are relevant to this discussion. Some species are cultivated as garden flowers, but these need not concern us here, since they are not known to cause pollinosis.

(1) *Amaranthus* (FIG 103) The pigweeds or amarantans occur throughout the United States, but are far more important in the west and particularly

the southwest, where they are more abundant, better developed, and more varied as regards the number of species found. The most important nationally is the common or redroot (beetroot) pigweed (*Amaranthus retroflexus*)—sometimes confusingly called "careless weed"—which is widely distributed in all cultivated areas of the country, especially in neglected gardens. Spiny amaranth (*A. spinosus*), also called prickly careless weed and soldier weed, likewise is widespread, but is chiefly important in the regions southward from Kansas and Colorado, and in Florida and neighboring states. Palmer's amaranth (*A. palmeri*) is for all practical purposes confined to the southwest, from Texas to southern California, and is here one of the leading offenders. In protected areas, it may bloom perennially. In this region as well as from Colorado to Oregon and Washington, prostrate pigweed (*A. blitoides*) is also found. Finally, tumbling weed or tumbleweed (*A. graecizans*)* is also widespread, but much more common in the Rocky Mountain and Pacific coast regions than elsewhere. Except as noted above, all the amarantans pollinate rather scantily from July to September.

(2) **Western water hemp** Western water hemp (*Achida tamariscina*), a coarse annual, occurs from eastern South Dakota to southern Illinois and Indiana, and in areas southward to Louisiana and Texas, as well as in western Mexico. However, it reaches its greatest development in Oklahoma and northern Texas, where it is one of the principal factors in pollinosis from late June to October. The closely related *Achida tuberculata*, found in parts of North Dakota, Minnesota, Wisconsin, Michigan, and Iowa, is of less importance.

The Goosefoot Family (Chenopodiaceae)—As already mentioned, this family is botanically allied to the pigweeds, and like these, is of far less consequence in the east than in the west. Four genera (*Chenopodium*, *Salsola*, *Kochia*, and *Atriplex*) are of major rank over large areas, but the lesser ones (*Dondia*, *Beta*, *Eurotia*, *Sarcobatus*, and *Allenrolfea*) merit brief consideration.

(1) *Chenopodium* The most widely distributed if not the most important representative of the entire family is lamb's quarters or goosefoot (*C. album*) (FIG 104). The shape of the larger lower leaves accounts for both the common and scientific names of the plant and its family. Related species are the nettle leaved goosefoot (*C. murale*), Mexican tea (*C. ambrosioides*) and its perennial relative, wormseed (*C. ambrosioides*, var. *anthelminticum*), which provides oil of chenopodium. All these are pernicious native North American weeds, occurring throughout the United States and Canada; they are particularly large and abundant in the southwest, where the soil tends to be salty and the seasons hot and dry. Their pollination is rather prolonged under such conditions, from June to October, although in the east it ceases in July or August. The oak leaf goosefoot (*C. glaucum*), with a pollination period in July and August, is of some significance in

* It should be pointed out that the name tumbleweed is also applied to Russian thistle, as well as to certain grasses that break off in the winter and are tumbled about by the wind.



FIG 104 LAMB'S QUARTERS (*Chenopodium album*)

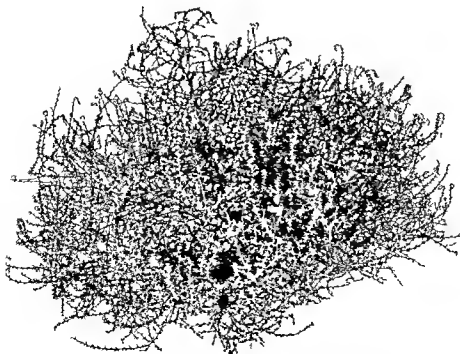


FIG 105 RUSSIAN THISTLE (*Salsola pestifer*)

the vicinities of Salt Lake City and Chicago. Many other species of *Chenopodium* exist, especially in the southwest and in California. Among them are narrow leaved goosefoot (*C. leptophyllum*), Watson's goosefoot (*C. watsoni*), mealy goosefoot (*C. incana*), sowbane (*C. murale*), and Jerusalem oak (*C. botrys*), the last named flowering from July to September.

(2) *Salsola*. Probably the most important hay fever plant in the entire goosefoot family, Russian thistle (*S. pestifer* or *S. kali*) (FIG. 105) is also called tumbleweed and saltwort. Although occasional specimens occur in the east, it grows largely west of a line from western Minnesota to western Texas, particularly from South Dakota to Colorado and southward to the Texas panhandle. It is especially well adapted to the semi-arid soil of the northwestern and mountain states. Its pollen is very abundant in the air at Denver. It pollinates from July to September, and in the region described is a prime offender.

(3) *Dondia*. Closely related to the Russian thistle is the sea blite (*Dondia*, formerly *Suaeda*), of which several species occur in the west and midwest, and particularly on the Pacific coast. Since its appearance resembles that of its relative, including its "tumbling" propensities, and since it has the same habitat but is a much more profuse pollinator, it is possible that some of the hay fever attributed to Russian thistle may actually be due to *Dondia* pollen. The species most often mentioned are the alkali blite (*D. fruticosa*), sea blite (*D. californica*) and ink bush (*D. suffrutescens*).

(4) *Kochia*. Burning bush (*K. scoparia*) also known as firebush, Mexican fireweed, or summer cypress, has much the same distribution as Russian thistle, but is most plentiful in Iowa, Colorado, Kansas, Nebraska, the Dakotas and neighboring states. It is sometimes planted in the east for its attractive red foliage, but is not sufficiently abundant to be troublesome. Where it has escaped from cultivation under conditions favorable for its growth and propagation, it is one of the major offenders. It constitutes a prime example of an ornamental plant becoming a weed. Observations in recent years indicate that it is spreading. Its pollen has attained significant levels of atmospheric pollution as far east as central Iowa, and is challenging both Russian thistle and ragweed in the middle Mississippi valley, where ragweed has always been dominant. Its pollination takes place from the end of July to mid-September. The related *K. americana*, called "red sage," has spread from central New Mexico through desert valleys from California to Colorado.

(5) *Atriplex*. Twenty seven species of the genus *Atriplex* are mentioned in the literature as causing hay fever, and are variously known as orache, saltbush, and shad scale. Like the other members of this family, the atriplexes are of importance only in the west. Although it has a scattered occurrence to the east, halberd-leaved orache (*A. patula* or *A. hastata*), also called spear scale, hastate atriplex, and fat hen, has little importance there. Other species accounting for considerable hay fever in the Rocky Mountain states, in parts of California, and especially in Arizona and New Mexico, are "bad scale," wing scale, or bushy atriplex (*A. canescens*), annual saltbush (*A. wrightii*), red orache or red scale (*A. rosea*), Australian saltbush

or fleshscale (*A. semibaccata*), bractscale (*A. bracteosa*), lenscale (*A. lentiformis*), and shadscale or spiny saltbush (*A. confertifolia*), and silver scale or silvery orache (*A. argentea*). Cross reactions between the species are not the rule, and although all are potential causes of hay fever and some are of local importance, most of them are not sufficiently abundant or do not produce sufficient pollen to account for very many cases. The various species pollinate at different times in the summer and fall, except the holly scale or desert holly (*A. hymenelstris*), which flowers from February to April in southern California.

(6) *Beta*. The common sugar beet (*Beta vulgaris*) is also a chenopod related to the atriplexes. Its pollen has been shown to be a cause of hay fever from early May to mid-June in those sections (for example, in Texas and Arizona) where it is intensively cultivated. The present increase in acreage devoted to it will probably enhance its importance. Patients clinically sensitive to the pollens of other chenopods are particularly likely to acquire sensitivity to beet pollen, but require specific therapy.

(7) *Eurotia*, *Sarcobatus*, *Allenrolfea*, and *Salicornia*. Three other species of the west, ranging from western Texas and adjacent states to Washington and western Canada, belong to this family: winter fat or sweet sage (*Eurotia lanata*), greasewood or chico (*Sarcobatus vermiculatus*), and burro weed, iodine bush, or pickleweed (*Allenrolfea occidentalis*). Although clinical data concerning them are meager, they are thought to be of some local importance, in arid districts only. The dates of their flowering are rather variable. In addition, the glasswort or samphire (*Salicornia ambigua*) has been suspected of causing hay fever in northwestern California.

The Plantain Family (Plantaginaceae)—Only one genus in this family is significant in relation to pollinosis, that which gives the family its name.

(1) *Plantain*. English or narrow-leaved plantain (*Plantago lanceolata*), also called rib grass and ribwort, as well as by at least sixteen other common names, is a familiar weed, widely distributed in lawns and waste fields, often in association with dandelions, throughout the United States and Canada (FIG. 106). It is more abundant in the midwestern and Pacific coast areas, and in the states adjacent to the District of Columbia, than elsewhere. Some authors group it along with the grasses because of its pollination dates and because the botanists once so classified it. Its pollen is anemophilous and quite abundant and buoyant. It is characterized by an extraordinarily prolonged pollination, running through most of the grass season and well into or even through that of the ragweeds. In most parts of the country, this goes on from April or May to October, and even later in Texas and the southwest. Much more of the pollen is shed in the earlier months of this period than in the later ones.

The related common, greater, or broad leaved plantain or henbane (*P. major*), is likewise found throughout the country, but is less important in pollinosis due to its scanty pollination. In southern Texas, a mixed type has been reported, neither English nor broad leaved. Several other species, including Rugel's plantain (*P. rugelii*), have some local incidence.

The Buckwheat Family (*Polygonaceae*)—In this family likewise only one genus requires consideration

(1) *Dock and sorrel* The two most important members of the genus *Rumex* are sheep sorrel or sorrel dock (*R. acetosella*) (Fig 107) also known as red or field sorrel or red dock and curly yellow sour or narrow dock (*R. crispus*) The broad leaved or litter dock

hymenosepalus) occurs only in the West in dry sandy areas from New Mexico to California

The Hemp Family (*Cannabaceae*)—Only two genera constitute this the smallest plant family pertinent to a discussion of pollinosis and each of them includes a weed of minor importance Both are considered by some authorities as belonging to the

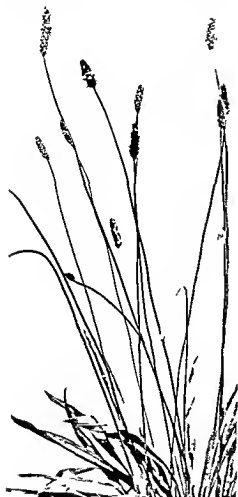


FIG 106 ENGLISH PLANTAIN (*Plantago lanceolata*)



FIG 107 SHEEP SORREL (*Rumex acetosella*)

(*R. obtusifolius*) is closely related to the latter and very similar in appearance All are perennial weeds sometimes erroneously classed as grasses because they pollinate at the same time as the latter They are probably in part insect pollinated All are widely distributed throughout the United States but are generally held to cause more cases in the midwest and far west They pollinate from May to July later in the south and west coast areas—the first named more abundantly Eleven other species are mentioned as occurring locally in various parts of the country The canagrace pie or sour dock or wild rhubarb (*R.*

mulberry family (*Moraceae*) or the nettle family (*Urticaceae*)

(1) *Hemp* True hemp (*Cannabis sativa*)—not to be confused with the unrelated western water hemp mentioned above—is the source of fiber for rope and sacking manufacture and of the outlawed narcotic marijuana or hashish It has escaped from cultivation on which was discontinued in this country by law some years ago and has become a troublesome weed in the lower Missouri River valley although isolated patches are to be found throughout the north central and eastern states as far south as Georgia and westward

to Kansas and Minnesota. In the vicinity of Omaha, where it has its greatest stand, it is said to account for 15 per cent of the pollen content of the air in the fall season, and 20 per cent of the cases of hay fever. Present plans to re-establish the hemp-growing industry in the United States, necessary because of the interruption of overseas supplies, may well increase this problem. Hemp pollinates rather abundantly from July to September.

(2) *Hop*. The hop (*Humulus lupulus*) is a twining or prostrate vine, often of considerable length, the pistillate flowers of which are the familiar hops of commerce, used to flavor malt liquors (beer). Since the hop is a dioecious plant there are individuals possessing only staminate flowers (the male) and those with only pistillate flowers (the female). Only the former can cause pollinosis. It grows in thickets and on river banks in scattered parts of the country east of the Rocky Mountains. Pollination dates vary from place to place but occur chiefly in July and August. The Japanese hop (*H. japonicus*) has escaped from cultivation and appears through the east, being reported from as far west as Chicago.

2. PLANTS AND PLANT PRODUCTS

We shall consider here the most important plants and parts of plants known to be capable of acting as inhalant allergens—with the exception, of course, of the pollens and odors of plants, since these are discussed in separate sections.

Cottonseed can cause allergic nasal and bronchial manifestations in individuals handling raw cotton. But the asthma of the cotton worker, which has been known for over a century, particularly in England, can be attributed to cottonseed only if skin or bronchial tests are positive. Not infrequently the true cause of the condition may be the molds that multiply rapidly in damp cotton. Moreover, P. A. Neal of the National Institute of Health has isolated from low-grade, dusty, stained cotton a "cotton bacterium" which he believes is responsible for numerous outbreaks of acute illness in rural mattress makers, resembling the mill fever, Monday fever, or gin fever common in cotton mill workers.

Another agent of exposure to cottonseed are cotton linters, the short fibers that cling to the cottonseed after the long fibers have been removed, inasmuch as they invariably contain particles of seed. Linters are widely used in padding, wadding, and batting, to make pads, cushions, comforts, and some mattresses and upholstery. Linters are also used for the

manufacture of certain varnishes, particularly those for coating metals, artificial leathers, and waterproofing. Cottonseed cake and meal are included in fertilizers and feed for stock, so that patients should avoid recently fertilized fields, barns, and feed supply stores. Cottonseed flour is sometimes used for human food, such as cereals, and in the manufacture of some gins. Although concurrent sensitivity is not invariable, most cottonseed-sensitive patients would do well to avoid foods prepared with cottonseed oil (see p. 313).

It must also be mentioned here that tests with cottonseed often elicit unusually strong local responses, occasionally accompanied by severe constitutional reactions. It is advisable, therefore, to begin with a scratch test, if this is negative, intracutaneous testing (with a 1:1,000,000 dilution initially) may be done. Clements²⁶⁹ has described an oral hyposensitization for cottonseed allergy. A cupful of cotton from the patient's mattress is extracted with glycerine-saline solution, and if a positive skin test is obtained after ultrafiltration, a drop of extract is taken in an ounce of water. If no untoward reaction occurs, the daily dose is gradually increased for about 24 weeks, and then a maintenance dose daily for one or two years. Iodides and dilute hydrochloric acid may be given at the same time.

Patients allergic to the protein of cottonseed on cutaneous tests will not be affected by the processed cotton in clothing, bed sheets, and pillowcases. In cases that show hypersensitivity to such manufactured products, it is probably attributable not to the cotton itself but rather to dyes and other finishing substances. Cohen and his associates²⁷⁰ have made the interesting observation that when raw cotton ages, the dust thus gradually formed contains a new allergen—probably identical with the "house dust allergen"—that is antigenically unrelated to cottonseed.

Kapok, derived from the seed hairs of certain tropical trees and widely used for stuffing pillows, mattresses, and upholstered furniture, not infrequently acts allergenically, especially in individuals who are hypersensitive to cottonseed. This is not difficult to under-

²⁶⁹ CLEMENTS, R. M. J. M. A. Alabama 11: 428, 1942.

stand, since there is a botanic relationship between the cotton plant and the kapok tree. According to Coca and Grove, some of the excitants of cottonseed and kapok seed are identical. Coulson Spies, and Stevens³⁷⁹ confirmed this by demonstrating three antigens common to cottonseed and kapok seed by immunologic (Schultz Dale and precipitin) methods, and concluded that hypersensitivity to kapok seed is probably induced by cottonseed contact. This does not mean that all individuals who are allergic to cottonseed necessarily react to kapok, and vice versa. However, since patients sensitive to cotton seed will often develop an allergy to kapok on prolonged contact with the latter, it should not be used as a substitute for cotton. Exposure to pure kapok fibers probably does not induce sensitivity to the seed.

Another seed that not infrequently shows a tendency to cross reactivity with cottonseed and kapok seed is flaxseed (*linseed*). Inhalant allergy, particularly asthma, that is due to flaxseed is usually evoked by fresh paints, varnishes, polishes, linoleum, oilcloth, imitation leathers, and printing and lithographing inks—all of which contain linseed oil. The condition may also be evoked by ground flax seed (for poultices or poultry feeds), as well as by flax straw used for rugs, mats and stuffing material. And Grant has demonstrated that flaxseed used in wave setting preparations can be the cause of asthma in the patron or in the hairdresser. Linen fabrics are probably not responsible for allergic symptoms.

Powdered *orris root* is a very common inhalant allergen. Because of its agreeable violet odor and its flesh color, it is widely employed in the manufacture of cosmetic and toilet articles, such as face, body, and tooth powders, rouge, cleansing creams, bath salts, scented soaps, mouth washes, sachets, dry shampoos, lotions, smelling salts, toilet waters, Eau de Cologne, and perfumes. Extracts are also employed in fumigating materials, adhesive plaster, candies, pastries, and soft drink syrups. Now that it has become more or less generally recognized that orris root and its oil not uncommonly act as allergens—especially in women—many manufacturers

have abandoned the use of it and indicate this on their labels. But the degree of the patient's hypersensitivity is sometimes so extreme that an attack (nasal or bronchial) is brought on for example merely by presence in the same room with a person using a cosmetic containing orris root. In these cases hyposensitization is indicated using the same methods as in treatment of pollinosis.

Patients sensitive to orris root (or perfumes—the two being frequently associated) are given the following instructions (Efron³⁷¹):

- (1) Use only the recommended unscented hypoallergenic cosmetics and to let preparations and unscented soap and talcs. Unscented sodium perborate may be utilized as tooth powder.
- (2) Other members of your household should also employ these preparations.
- (3) Remove all scented cosmetics and toilet preparations from the house.
- (4) Do not take dry shampoos.
- (5) Avoid contact with perfumes.
- (6) Spend as little time as possible in beauty parlors and at cosmetic counters.
- (7) Do not use prepared mouth washes. Salt water may be substituted.
- (8) Do not permit flowers which have scents in the house. Do not wear or smell such flowers and avoid the odors of the flowers of *ligustrum*, *jasmine*, *honeysuckle*, etc. If these plants grow around your house, either clip the buds before they bloom or remove the plants entirely.

Pyrethrum is the dried powdered flower of the pyrethrum plant, a member of the chrysanthemum family. It is widely employed in the preparation of insect powders and sprays and is thus extensively used not only in the home for combating moths and other insects but especially in theaters, motion picture houses, shops and warehouses. Since insecticidal preparations are used primarily in the summer, pyrethrum allergy is usually seasonal, although nonseasonal symptoms may occur. Ragweed sensitive patients frequently react to pyrethrum. The pyrethrins derived from pyrethrum, are even more potent as an insecticide, their allergenic properties have not yet been investigated. Commercial pyrethrum contains three toxic principles: an ester with insecticidal properties which may cause poisoning, a lipid or oleoresin, which may cause dermatitis, and an allergen related to ragweed pollen, which is responsible for the respiratory allergic manifestations (Feinberg³⁸⁴).

Derris root, the root of a tropical shrub, is

used in flea powders, and was the cause of asthma in 2 cases reported by Weston. Oliveira Lima⁹⁷² observed asthma and nasal symptoms from an insect spray made from the *Lonchocarpus* or *limbo*, a closely related plant of the *Leguminosae* family which gives rise to cross reactions with derris.

Jute, a fiber obtained from *Corchorus*, grown in India, can become an allergen for persons occupationally exposed to its dust (Stevens and Jordani⁹⁷³). One of us found burlap, a material made from jute, to be the cause of a long-continued asthma in a truck driver, and it was possible to control the condition by injections of an extract of burlap. Jute is also found in inexpensive upholstered furniture, domestic rugs, and carpet padding.

Lycopodium, the spores of the moss *Lycopodium clavatum*, is a fine white powder, mainly used by druggists to prevent pills from conglomerating, and also employed to powder the walls of forms in metal castings. It is sometimes used as a dry shampoo. Asthmatic attacks attributable to this powder have been reported by Peshkin, Sticker, and Hanhart.

The powdered roots of *ipecacuanha*, *rhubarb*, and *poke* are occasionally causes of asthma or rhinopathy in druggists. The senior author observed asthma in a pharmacist caused by inhalation of powdered *digitalis*.

Papain (caroid) is a potent antigen, acting chiefly in pharmacists by inhalation (Osgood⁹⁷⁴). However, as in 1 case reported, sensitization can also occur from local application to granulation tissue. In allergized individuals, reactions can also be elicited by ingestion. Papain has several uses medicinally, industrially (especially in brewing and tanning), in dentifrices, chewing gum, and in food preparations.

The dust of *castor beans* may become an allergen to individuals living in the neighborhood of a castor oil mill (Figley and Elrod⁹⁷⁵) or working in fertilizer factories (Zerbst⁹⁷⁶) or laboratories in which these beans are extensively handled. Skin testing with this allergen is to be carried out very cautiously, beginning with the scratch method. In addition to the

medicinal and multitudinous industrial uses of castor oil, castor bean meal is in demand as a fertilizer and farm workers in contact with it have been sensitized. Ratner⁹⁷⁶ succeeded in allergizing guinea pigs by inhalation of dry castor bean dust.

Hypersensitiveness—expressed by asthma and rhinopathy—to *coffee beans* has occasionally been observed in workers in coffee factories, in persons who handle sacks of coffee, and in grocers. This hypersensitiveness is mediated sometimes by the protein of the coffee beans and sometimes by the aromatic volatile oils (p. 511). Sensitivity to the dust of *chicory*, *hops*, and other beverage ingredients has been described. Hypersensitiveness to the dust of *tea* has been observed by Sticker and by Klewitz in individuals who were occupationally exposed to massive contact with tea.

Tobacco, in view of the millions of smokers, must be said to act as an inhalant allergen only rarely. However, it plays a relatively far more important rôle among individuals who work with tobacco. Furthermore, there have been many reports of so-called hypersensitiveness to the nonspecifically irritating or toxic factors contained in tobacco smoke or in the combustion by-products of the paper. Positive skin tests with tobacco need not necessarily be specific (see p. 832). In addition, as Vaughan²¹ has pointed out, the wrappers of cheap cigars are usually stuck together with a gum tragacanth or corn syrup paste, hypersensitiveness to these is occasionally observed. However, allergy to tobacco itself can unquestionably be a cause of asthma. Thus, the senior author has observed the case of a Turkish woman whose asthma appeared only when she was on her estate, which was adjacent to a large tobacco plantation. Asthma due to tobacco smoke or to work in tobacco factories has been described by Walker, Feinberg, Jiménez-Díaz, and Rich. The relationship of tobacco sensitivity to various peripheral vascular diseases is as yet unsettled.

Occasional patients, as Vaughan²¹ demonstrated, are hypersensitive not to tobacco itself, but only to tobacco smoke. This was

⁹⁷² OLIVEIRA LIMA, A. *J. Lab. & Clin. Med.* 29: 939, 1944.

⁹⁷³ STEVENS, F. A., and JORDANI, L. *J. Allergy* 9: 610, 1938.

⁹⁷⁴ OSGOOD, H. *Ibid.* 16: 215, 1945.

⁹⁷⁵ ZERBST, G. H. *Indust. Med.* 13: 552, 1944.

⁹⁷⁶ RATNER, B. *J. Allergy* 2: 1, 1950.

confirmed by exhaustion tests by Pipes⁹. It is recommended therefore that in cases in which tobacco is suspected tests be made not only with tobacco antigen but also with an extract of tobacco smoke. The simplest method of preparing tobacco smoke extract consists according to Vaughan in having the exhaled smoke bubbled through Coca s fluid which is then sterilized by filtration. In Pipes⁹⁷⁷ series of allergic patients about 9 per cent gave definite histories of their respiratory symptoms being precipitated or aggravated by exposure to tobacco smoke and approximately 13 per cent gave positive endermal tests to tobacco smoke extracts.



FIG 108 NEURODERMATITIS DUE TO INHALATION OF RYE FLOUR

Cereal flours such as rye wheat oat corn barley and buckwheat flour are frequently the cause of severe rhinopathy and asthma in millers bakers confectioners threshers grocers and less often in housewives. We have also observed a severe neurodermatitis (Fig 108) of many years duration that was proved to be due to inhalation of rye flour. The patient was a baker's daughter whose bedroom was adjacent to the bakery. The diagnosis was based on the fact that the girl became free of symptoms on remaining away from home and that nasal insufflation of a small quantity of rye flour produced severe itching and constitutional symptoms requiring epinephrine injections.

However the possibility of a physical hypersensitiveness to the silicated particles of the hull of the grain must also be borne in mind in cases of asthma in which the attacks appear while the grain is being thrashed loaded cleaned or otherwise handled (see p 433). In order to determine whether or not the case is one of hypersensitiveness to the flour itself the patient may sniff in a small quantity of the suspected flour.

Grain mill dust according to Wittich⁹ contains in addition to plant particles also smuts rusts common air molds pollens of various kinds bacteria and insect fragments.

Mention must also be made of the sawdust of numerous woods such as cedar pine fir box mahogany and birch. In all these cases appropriate tests must be made in order to determine whether the hypersensitiveness is in relation to the wood itself or to some contaminant such as molds and mites often found in the bark or to the volatile oils or the respective oleoresins. The exact identification of the causal factor is obviously of prime importance for treatment.

Straw hypersensitiveness is not exceedingly rare in agricultural sections and produces chiefly asthma and rhinopathy. In such cases it will be necessary to determine whether the allergy is in relation to the straw protein itself or to remaining pollens or to smuts rusts and molds.

Dean⁹⁷⁸ reported a case of severe perennial rhinopathy due to *Spanish moss* (*Tillandsia usneoides*) a plant native to the southern states the fiber of which is used in upholstery stuffing and in packing fruit for shipment.

Bagasse the broken stalks of sugar cane after the sugar has been extracted is employed in the manufacture of a durable insulating board. Sensitization to the protein antigen contained in its dust gives rise to an acute afebrile inflammatory lung disease of variable duration unrelated to silicosis and called bagassosis (Castleden and Hamilton Paterson⁹⁷⁹).

Vegetable gums may act as allergens by inhalation ingestion injection or contact but the first is the most common route and

⁹⁷⁸ DEAN G. A. *J. Allergy* 14: 340, 1943.

⁹⁷⁹ CASTLEDEN L. I. M. and HAMILTON PATTERSON J. L. B. *M. J.* 24: 8, 1942.

respiratory symptoms predominate. Gelfand³⁵⁰ has reviewed the literature on this subject, and has gathered a valuable list of the known sources of possible contact with allergenic gums. Exposure is usually occupational, in the industries mentioned below. Bobner and his associates³⁵¹ reported 10 cases of asthma due to *acacia* (gum arabic). These patients were all printers who were exposed to the *acacia* offset sprays used in the industry. Asthma in a candy maker exposed to dust consisting largely of *acacia* was described by Spielman and Baldwin³⁵² Bullen,³⁵³ Feinberg,³⁵⁴ and Figley³⁵⁵ called attention to *karaya* or Indian gum, which is used as the base of wave-setting preparations. It is inhaled from the flaking of the dried material when the hair is combed. Gelfand³⁵⁰ reported a case of *tragacanth* sensitivity in a worker in a gum factory and showed that in addition to the botanic relationship there is an antigenic one between it and *acacia*.

3. SCENTS OF PLANT ORIGIN

Clinical and experimental evidence proves that odors can act as inhaled allergens in certain cases. Among these are the scents of flowers, fruits, and resins, and the odors of food of plant origin. Odors of foods of animal origin and chemical odors are considered in other sections of this chapter.

Aromatic substances are characterized by their volatility and strong odor, and belong to the group of ethereal oils. The technologist defines ethereal oils as products extracted from plants by a common method, such as steam distillation; these oils are distinguished by their characteristic odors. The ethereal oil is usually composed of a variety of compounds, many of which are still unidentified. Most of them are derivatives of terpene ($C_{10}H_{16}$), but nitrogenous substances such as anthralin acid esters, indole, skatole, and mustard oils are also frequently found. It has been assumed that the latter group may

be especially significant in cases of hypersensitiveness.

The French scientist H. Devaux devised a photographic method to demonstrate that odoriferous substances give off minute material particles (Fig. 109), which he called *osmyls*. From these experiments he concluded that we smell a flower, for instance, because minute particles originating from the petals strike the sensitive membranes of the nose. Part of the evidence for the conclusion that the odors of the blossoms of various trees, shrubs, and flowers may act as allergens depends on the demonstrated fact that they can elicit typical hay fever and asthma symptoms. This will be found discussed in detail in the section on the etiology of hay fever (p. 511).

The writers observed quite a few cases that were proved to be due to volatile oils. However, it has not been possible to determine which ingredients of the ethereal oils of the blossoms cause hay fever, since chemists are not yet able to fractionate the ethereal oils of roses, lilac, jasmine, etc., into stable constituents.* However, one might speculate that the unstable proteins present in the ethereal oils may be responsible for the allergenic effect.

The senior author³⁵⁶ therefore studied the problem in cases in which the patients were sensitive to other ethereal oils, such as sage (*Salvia officinalis*), that are capable of chemical fractionation. It was found that the allergenic principle was not any of the known constituents of sage, including sage oil, but a substance soluble in petroleum ether and volatile on steam distillation. This component, the chemical nature of which is as yet unknown, mediates the odor and in all probability constitutes the allergen in question.

It should be stated here that patients who are hypersensitive to the smell of roses, for example, but not to the pollen, frequently show hypersensitiveness to other pollens, for instance those of grasses.

As an unusual case of sensitivity to odor may be mentioned Zalon and Kahn's³⁵⁷

³⁵⁰ GELFAND, H. H. *J. Allergy* 14, 235, 1943.

³⁵¹ BOBNER, C. B., SHELTON, J. M., and TREND, J. W. *Ibid.* 12: 290, 1941.

³⁵² SPIELMAN, A. D., and BALDWIN, H. *Ibid.* 4, 451, 1933.

³⁵³ BULLEN, S. S. *Ibid.* 5: 151, 1934.

³⁵⁴ FEINBERG, S. M. *J. A. M. A.* 105, 55, 1935.

³⁵⁵ FIGLEY, K. D. *Ibid.* 144: 747, 1943.

* Synthetic oils that imitate the odors of the plants in question cannot be used in these investigations, as they are chemically entirely different from the natural ethereal oils.

³⁵⁶ CRAWFORD, E. *J. Allergy* 13: 387, 1942.

³⁵⁷ ZALON, S. J., and KAHN, J. B. *Arch. Dermat. & Syph.* 52, 11, 1945.

patient who had chronic urticaria of six years' duration due to the use of perfumes

Besides hypersensitiveness to odoriferous buds and flowers bushes and trees there seems to be also a hypersensitiveness to the essential oils of conifers as well as to the resins of other trees. Thus rhinopathies and asthmas may be caused in carpenters and wood workers by coniferous trees and in house painters and others by turpentine. Derbes

strongly odoriferous orris root oil (in scented soaps toilet water smelling salts hair tonic) to essential oils of eucalyptus and camomile both of which are used for inhalation to aloe valerian parsley hop and dill as well as to camphor peppermint and incense. The instructions to the patient for the avoidance of orris root and common scents are given above. Allergy to linseed oil as described by Sticker is less frequent; he reported that a colleague of



FIG. 109. PHOTOGRAPH OF EFFECT PRODUCED BY ODOR OF ROSE PETAL (DEVALX TECHNIC)

Central outline represents position of rose petal suspended over mercury dusted with talc. (European Picture Service)

and Engelhardt⁹⁸⁸ reported the invariable production of an attack of asthma associated with urticaria in an 11 year old boy within 15 to 30 minutes after exposure to the fumes of fresh paint. While the asthma subsided within 24 hours the urticaria persisted 3 or 4 days. In a series of cases of allergic uropathy Thomas and Wicksten⁹⁸⁹ include one of frequency and painful urination and another of dysuria and cystitis due to paint fumes. We must also mention hypersensitiveness to the

his suffered from a severe rhinopharyngitis upon entering places that were freshly painted with linseed oil. Smelling linseed oil for a few seconds caused quick blanching of the nasal mucosa; smelling for a few minutes caused inflammation lasting for twenty four hours.

Finally allergy to the smell of vegetable foods has to be kept in mind. The hypersensitiveness may be elicited by the odor of the raw foodstuffs such as garlic and onion as observed by the senior author. Henson⁹⁹⁰ described garlic inhalation as the cause of

⁹⁸⁸ DERBES, V. J. and ENGELHARDT, H. T. *South. A. M. J.* 37: 729, 1944.

⁹⁸⁹ THOMAS, J. W. and WICKSTEN, V. P. *Ann. Allergy* 2: 396, 1944.

⁹⁹⁰ HENSON, G. E. *J. Fla. da M. A.* 27: 86, 1940.

asthma in a patient who worked in a sausage factory where powdered garlic was used. Zohn⁹⁹¹ reported sensitivity to spinach by inhalation, and Horesch⁹⁹² asthma in a 2-year-old boy due to the presence in the same room of white potatoes, fresh or canned, and especially while cooking. The latter⁹⁹³ also observed a case of infantile dermatitis due to cabbage that could be exacerbated by the odor of cooking cabbage, as well as 8 other similar cases due to animal foods. He points out that recurrences deserve strict elimination diet may readily be due to such unrecognized inhalant exposure.

The senior author also treated a woman who developed severe rhinopathy and asthma a few weeks after accepting a position in a coffee store. Twenty-four hours after hospitalization her attacks disappeared, though no treatment had been instituted. Smelling of a small bag of coffee for only three minutes caused several nasal and bronchial attacks after a very short time. Sternberg and Sorrell⁹⁹⁴ observed rhinopathy in a restaurant employe from the fumes of coffee. Sticker⁹⁹⁵ reported the case of the Polish king Jagello, in whom the smell of apples produced attacks of asthma. In other patients the odor of food only during the process of cooking is operative. Thus, Feinberg and Aries⁹⁹⁶ described instances of asthma due to volatile substances given off in the cooking of peas, beans, and lentils. To demonstrate the volatile nature of the reacting substance, Feinberg exposed shallow dishes of Coca's solution at distances of 30 inches and 5 feet, respectively, from a pot in which dried peas were being cooked. Skin testing with the first solution gave a definite reaction of the same strength as that induced by an extract of a pea in a dilution of 1:10,000,000, while the second elicited only a faint reaction.

D. FUNGI

There is an increasing realization of the importance of fungi, particularly the spores of the common air molds, smuts, and rusts, as inhalant allergens. These molds occur in the air and on grass and trees, as well as in

dust. Widespread as they are, they seem to cause allergization only when the exposure to them is rather intense, such as musty cellars or damp houses, or when the atmospheric pollution with mold spores is at its height.

The following conditions must be fulfilled before a case can be definitely diagnosed as one of hypersensitiveness to mold: (1) proof of the presence of the mold in the immediate environment (home, place of work), (2) freedom from symptoms when away from this environment or when the atmospheric concentration of mold spores falls; (3) onset of an attack following exposure (nasal or bronchial test) or injection, (4) definitely positive cutaneous reaction to an extract made of spores, (5) passive transfer of the cutaneous hypersensitiveness by the Prausnitz-Kuestner method.

For specific diagnosis major dependence should be placed on the scratch test, employing either the dry, killed, and powdered mold, preferably harvested when it is sporulating strongly, or a concentrated (1:20 or 1:50) liquid extract. A positive reaction is of the immediate wheal type, such as is obtained with pollens or epidermals. Only if the scratch test is indecisive or negative should an intracutaneous test be performed, usually with a 1:1000 extract. A positive scratch test reaction to fungi almost always signifies clinical sensitivity, while a positive intracutaneous test is less conclusive. In an occasional instance, a delayed reaction is the only evidence of sensitivity, although in some cases both immediate and delayed responses are observed. Failure to obtain skin reactions is, in itself, an inadequate criterion for ruling out fungous sensitivity.

The difficulties of preparing suitable extracts of molds for intracutaneous testing are illustrated by the experiments of Prince and Morrow.⁹⁹⁷ There is evidence that a considerable portion of the antigenicity is lost in the process. Browning⁹⁹⁸ found that positive skin tests to mold extracts are significant only after the irritating qualities and the diagnostic efficiency of the extracts have been determined. The diagnostic reliability of even the nonirritant extracts ranged only from 60 to

⁹⁹¹ Zohn, B. *J. Allergy* 8: 381, 1937.

⁹⁹² Horesch, A. *J. ibid* 15: 147, 1944.

⁹⁹³ Sternberg, L., and Sorrell, A. H. *New York State J. Med* 41: 1649, 1941.

⁹⁹⁴ Feinberg, S. M., and Aries, P. L. *J. A. M. A.* 98: 2280, 1932.

⁹⁹⁵ Prince, H. E., and Morrow, M. B. *Ann. Allergy* 2: 493, 1944.

⁹⁹⁶ Browning, W. H. *J. Allergy* 11: 231, 1943.

70 per cent. A group of investigators⁹⁹⁷ using specially prepared extracts obtained less than 3 per cent positive scratch test reactions in patients whose symptoms could be attributed to fungi.

When the skin tests are questionable or negative, and the clinical history nevertheless suggests fungous allergy, mucous membrane tests (conjunctival nasal or bronchial) should be tried. Conjunctival tests are performed by placing a drop of the concentrated extract or a speck of the fine powdered pellicle into the conjunctival sac. The typical vascular response, the edema of the conjunctiva, and the itching combine to produce a positive reaction. Chobot and his associates⁹⁹⁸ prefer the ophthalmic test as a means of checking the clinical significance of a positive skin test. The nasal test is carried out by direct application of a solution of the dry powder into the nose or by insufflating the material from a cotton applicator, platinum loop, or tooth pick. Bronchial testing (see p. 185) is done by atomizing a solution or the fine powder into the trachea. A variation of the last method is to place the patient in a closed room where fungous spores are disseminated by an electric fan. At present, all suspected fungi should be used for testing, since no common antigen has as yet been found although certain group relationships have been recognized.

Any remaining skepticism concerning the allergenic importance of the molds has long since been dissipated by the observations of a number of competent observers conforming to the criteria given above. Thus Dutton⁹⁹⁹ reported asthma occurring in a woman while picking beans which were demonstrably parasitized by *Alternaria*, symptoms were controlled by absence from the bean patch, and skin and passive transfer tests with this mold were strongly positive. Moreover, Blumstein¹⁰⁰⁰ was able by provocative tests by means of nasal insufflation of powdered mold extract to reproduce in 9 cases hay fever or asthma like symptoms similar to those complained of by the patients.

1 COMMON AIR MOLDS

Air borne mold spores must take their place along with pollen and dust as an important cause of mhalant allergies. Feinberg¹⁰⁰⁰ is of the opinion that molds rank second to pollen as the cause of nasal allergy in Chicago and its vicinity.

Molds are a subdivision of fungi and are known as *Thallophytes* in the plant kingdom. The thallophytes are characterized by their growth in irregular plant masses not differentiated into roots, stems, and leaves like higher plants. Such a mass of plant tissue is called a *thallus*. Fungi are devoid of chlorophyll and depend for food on organic matter synthesized by other organisms.

Fungi are subdivided into four main groups or classes according to whether the vegetative part or mycelium is septate or whether the reproductive part (the spores) is sexual or asexual.

(1) The *Phycomycetes* characterized by nonseptate mycelium and asexual spores in a sporangium and sexual spores called zygospores.

(2) The *Basidiomycetes* characterized by a septate mycelium and sexual spores basidiospores borne externally on the mother cell or basidium and attached by a stigma.

(3) The *Iscomycetes* characterized by a septate mycelium. The conidia or asexual spores are free on fruiting structures or develop directly from the mycelium. The sexual spores are borne within the mother cell or ascus.

(4) *Fungi imperfecti*, characterized by a septate mycelium. The asexual spores are located on various types of conidiophores. No sexual spores have been discovered, therefore the life history is incomplete. Most human pathogens fall in this group.

A clear distinction should be made between molds acting as infecting agents and those acting as allergens. Pratt¹⁰⁰¹ presented the problem in the following manner. In the first instance the molds behave like bacteria of low virulence and produce infections of the lungs, body cavities or skin. In the second instance, the molds are entirely nonpathogenic and act not as infectious agents but as antigens,

⁹⁹⁷ Committee of Allergists for the Study of Unknown Causes of Hay Fever and Asthma. *Ann. Allergy* 1: 51, 1943.

⁹⁹⁹ DUTTON, L. O. *Letters Internat. Core Club of Allergy*. Series 8: 15, 1945.

¹⁰⁰⁰ BLUMSTEIN, C. I. *Ann. Allergy* 3: 351, 1945.

¹⁰⁰⁰ FEINBERG, S. M. *Journal Lancet* 57: 87, 1937.

¹⁰⁰¹ PRATT, H. N. *New England J. Med.* 219: 782, 1938.

after the manner of pollen and other air-borne allergens. When a mold acts as an infecting agent, an intracutaneous test made with its extract will produce a delayed tuberculin type of reaction. When the mold acts as an allergen, mold extract will produce an immediate wheal reaction. While Pratt's concept is attractive, it requires experimental and clinical corroboration, since it does not correspond with the known facts of bacterial allergy. It must be stated, however, that most of the allergenic molds are nonpathogenic for man, in the sense of producing actual infection, and even for plants.

The following fungi were found by reliable authors to act as allergens in certain cases:



FIG. 110. ALTERNARIA SMEAR (X 550)
(Courtesy Dr. N. Schaffer)

Alternaria (FIG. 110), *Aspergillus* (FIG. 111), *Chaetomium*, *Cephalosporium* (FIG. 112), *Cephalothesium*, *Cladosporium*, *Fusarium* (FIG. 113), *Helminthosporium* (FIG. 114), *Hormodendron* (FIG. 115), *Monilia*, *Mucor* (FIG. 116), *Penicillium* (FIG. 117), *Rhizopus* (FIGS. 118, 119), rust, smut, *Torula*, yeast.

The first description of respiratory allergy due to the inhalation of fungous spores is generally credited to van Leeuwen.¹⁰⁰² However, Blackley¹⁰⁰³ in 1873 described inhalation experiments on himself with spores of *Chae-*

tomium and *Penicillium* which resulted in such severe symptoms that he abandoned this line of investigation. In Holland, where it is especially damp, van Leeuwen found that 50 per cent of his asthma patients gave positive reactions to skin tests with *Aspergillus*, *Mucor*,



FIG. 111. ASPERGILLUS (X 250)
(Courtesy Dr. N. Schaffer)

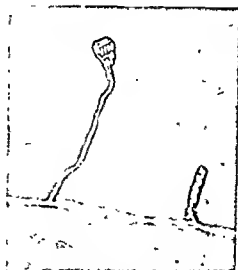


FIG. 112. CEPHALOSPORIUM (X 550)
(Courtesy Dr. N. Schaffer)

or *Penicillium*, while these same individuals were free from symptoms as long as they remained in an allergen-free chamber. Hopkins et al.¹⁰⁰⁴ evoked an asthmatic attack in a susceptible patient by means of a nasal spray

¹⁰⁰² LEEUWEN, W. S. VAN. Proc. Roy. Soc. Med. (Sec. Therap. & Pharm.) 17: 19, 1921.

¹⁰⁰⁴ HOPKINS, J. G., BENHAM, E. W., and KESTEV, B. M. J. A. M. A. 94: 6, 1930.

with *Alternaria* extract Hansen¹⁰⁰¹ produced asthmatic symptoms by having patients inhale spores of the molds to which they had reacted on skin testing. He also showed that patients frequently react only to the particular fungus growing in their own environ-

et al.¹⁰ and Pratt¹⁰²—in which the importance of molds in rhinopathy and asthma is stressed. The term sporosis was suggested to serve as the general designation of inhalant allergy caused by fungous spores.

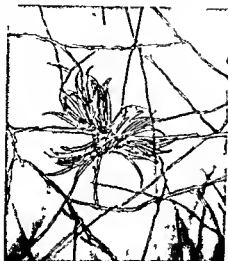


FIG 113 *FUSARIUM*
(Courtesy Dr N. Schaffer)

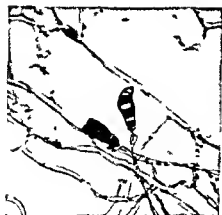


FIG 114 *HELMINTHOSPORIUM*
(Courtesy Dr N. Schaffer)



FIG 115 *HORMODENDRON*
(Courtesy Dr N. Schaffer)



FIG 116 *MUCOR* SPORES IN SPORANGIUM (X 550)
(Courtesy Dr N. Schaffer)

ment and not to spores obtained from other cultures. Numerous reports have since appeared—notably those by Durham¹⁰⁰³, Fernberg and Little¹⁰⁰⁶, G. T. Brown¹⁰⁰⁷, Waldbott

For a better understanding of the problem and for adequate management of his patients it is important that the physician be cognizant of the sources of the air-borne mold spores. Prince¹⁰¹⁰ has prepared the following list:

¹⁰⁰¹ HANSEN K. Verhandl. d. deutsch. Gesellsch. f. inn. Med. 40: 204, 1923.

¹⁰⁰³ DURHAM O. C. J. All. & Hyg. 8: 480, 1937.

¹⁰⁰⁶ FERNBERG S. M. and LITTLE H. T. Ibid. 7: 119, 1946.

¹⁰⁰⁷ BROWN G. T. Ibid. 7: 452, 1936.

¹⁰⁰⁸ WALDBOTT G. L., ARCHER M. S. and A. KLEY A. B. J. Mich. Gen. M. Soc. 39: 645, 1940.

¹⁰⁰⁹ PRATT H. N. J. Ped. at 14: 234, 1939.

¹⁰¹⁰ PRINCE H. E. 1944 Regional Conference No. 9. Am. Coll. All. & Im.

Soil is the most universal habitat for molds. Soil fungi play a predominant part in the decomposition of proteins and other organic matter returned to the soil in plant residues. Most of the common forms such as *Penicillium*, *Aspergillus*, *Fusarium*, *Alternaria*, *Helminthosporium*, *Hormodendrum*, and the *Mucorales* are thus widely distributed.



FIG. 117 *PENICILLIUM* (X 530)
(Courtesy Dr. N. Schaffer)



FIG. 118 *RHIZOPUS* SPORANGIA (X 100)
(Courtesy Dr. N. Schaffer)

Plants may be infected with parasitic fungi. Feenberg¹⁸⁴ holds that most of the allergenic fungi are plant saprophytes, living mainly on dead or injured plants, hence, these are important in agricultural areas, especially in the major grain belts, as well as in certain urban districts where much grain is handled, as in grain elevators, flour and feed mills, etc.

Citrus fruits, cured hams, and other foods may become heavily molded and produce great numbers of spores. *Penicillium italicum*, *P. digitatum*, *P. expansum* and *P. notatum* are commonly encountered.

Mildew of textiles is generally due to various species of *Aspergillus* or *Penicillium* introduced in raw material during manufacture or acquired in exposure to air in damp environments: awnings, tents, draperies, window shades, wallpaper and the canvas beneath it, etc., may furnish much mold growth in damp districts.

Upholstered furniture, especially that containing kapok and mattresses which contain raw cotton, furnish excellent substrata for mold growth. Colored stains in raw cotton may be due to *Fusarium*, *Cladosporium*, or *Aspergillus*, tethering or loss of strength to *Aspergillus fumigatus*, *Cladosporium herbarum*, *Stemphylium*, *Chaetomium* and *Penicillium*. Since either of these phenomena lowers the quality of the cotton, it follows that the cheaper grades generally used in bedding or upholstery may contain much infested material from the raw product.



FIG. 119 *RHIZOPUS* (X 100)
(Courtesy Dr. N. Schaffer)

Wool may be a source of *Penicillium* and *Aspergillus*. Manila hemp may deteriorate from *Aspergillus fumigatus*, *P. flavus* and *P. niger*.

Leather articles such as shoes and gloves, frequently become molded in damp climates.

Common bread mold *Monilia sitophila* occurs in bakeries and in many homes, it produces very fine spores in abundance and may be a potent allergen.

The quantity and species of molds present in a given environment are largely determined by geographic, climatic, and atmospheric conditions. Thus, Fraenkel¹⁸¹ showed that in Germany 16 per cent of all asthmatic individuals gave positive skin reactions to a mixed fungous extract, as compared with 53 per cent in England. This is readily understood in view of the rather dry climate of central Europe, as contrasted with the often rainy and damp

¹⁸¹ FRAENKEL, E. M. Brit. M. J. 2, 68, 1938

weather prevailing in the British Isles. In America, the greatest variety of conditions is encountered. For example, in Seattle, according to Schonwald's¹⁰¹² investigations, there is an average humidity of 85 per cent in the morning and 51 per cent in the evening while the corresponding figures about 400 miles in land are 42 and 27 per cent. To mention only a few significant findings, Schonwald reported that 77 per cent of asthmatic patients in Seattle gave positive skin reactions, while Feinberg¹⁰⁰⁶ stated that in Chicago only 28 per cent of such individuals reacted, although more recently he¹⁰¹⁴ gave the figure 40.9 per cent, but in an admittedly selected group of cases. Of 406 patients tested by Blumstein⁹⁹⁹ in Philadelphia, 169 gave positive skin reactions to one or more of 13 mold extracts, and 12 displayed clinical sensitivity to a nasal provocative test. However, all of the latter had seasonal symptoms, and constituted 9 per cent of the seasonal group tested. The offending molds, in the order of their importance, were *Alternaria*, *Hormodendrum*, *Monilia*, *Helminthosporium*, *Cephalosporium*, and *Mucor*. In San Antonio, Texas, Hampton and Lowe¹⁰¹³ found 57 mold reactors in a group of 358 cases of allergy, 54 of them with respiratory symptoms. *Alternaria* was the chief offender, followed in order by *Spondylocadium*, *Helminthosporium*, and lastly *Hormodendrum*, although the last was the most commonly encountered air borne spore in that vicinity. Lamson and Rogers gave the figure 12 per cent for Los Angeles and Balyeat's average for Oklahoma was a little over 1 per cent. In England, according to Fraenkel,¹⁰¹⁵ 66 per cent of a group of asthmatic patients reacted to scratch tests with one or more mold extracts, the majority to *Sporotrichum* types and *Cladosporium* and with decreasing frequency to *Penicillium*, *Aspergillus*, *Mucor*, and *Monilia*. Prince and Morrow¹⁰¹⁶ demonstrated that individuals hypersensitive to molds have an exacerbation of symptoms when the wind comes from the direction of neighboring swamps. Simon¹⁰¹⁷ reported a case of con-

junctivitis due to an allergic reactivity to the spores of air borne fungi.

Moreover, mold allergy is occasionally an occupational hazard. Thus Cobe¹⁰¹⁷ and Bernton and Thom¹⁰¹⁸ report that asthma in certain tomato growers was found to be due to *Cladosporium*, a fungus found on the leaves of the tomato plant.

Finally, the allergen may be the product of the action of molds on another substance. Wagner and Rackemann¹⁰¹⁹ demonstrated that the active allergic principle in old kapok depends on the interaction of the kapok and the molds growing in it, kapok and mold extracts, separately, did not provoke allergic reaction. The writers have observed a far higher incidence of allergy to molds in the Main Line districts in the vicinity of Philadelphia than in the suburbs situated to the north on higher ground. Furthermore, the incidence is relatively higher in old homes with damp cellars, and in houses along rivers, creeks and ponds. Mold asthma is encountered with striking frequency in cotton weaving mills where the damp cotton is sometimes heavily covered with mold and where fungi flourish in the finishing material composed of flour and clay. Weaver's cough" at times reached such epidemic proportions in England that the mills had to be closed down for a while (Midleton¹⁰²⁰).

However, the studies of Feinberg and of Durham indicate that air borne fungi may also be of importance in dry climates. Moreover, investigations made in airplanes have shown the presence of molds at altitudes as high as 18,000 feet (Brown¹⁰⁰⁷).

Surveys of the air borne fungous spores in a locality can be conducted by the identification of the spores on slides exposed to gravity fall for twenty four hours or to impingement apparatuses for shorter periods just as with pollens, or by identification of the colonies after suitable exposure of plates containing nutrient media (Sabouraud's, wort agar, or potato dextrose agar). A method¹⁰²¹ has been devised combining special sampling of the slides under microscopic guidance with special

¹⁰¹² SCHONWALD P. J. Allergy 9: 175 1938.

¹⁰¹³ HAMPTON S. F. and LOWE E. P. b d 16: 101 1945.

¹⁰¹⁴ FRAENKEL E. M. Br t M J 2: 14 1945.

¹⁰¹⁵ PRINCE H. E. and MORROW M. B. South M J 30: 751 1937.

¹⁰¹⁶ SIMON F. A. J. A. M. A 110: 440 1938.

¹⁰¹⁷ COBE H. M. J. Allergy 3: 389 1932.

¹⁰¹⁸ BERNTON H. S. and THOM C. b d 8: 363 1937.

¹⁰¹⁹ WAGNER H. C. and RACKEMANN F. M. Ann Int Med 11: 505 1937.

¹⁰²⁰ MIDLETON E. L. J. Indust Hyg 8: 428 1926.

cultural methods, thereby permitting more accurate identification as well as the preparation of extracts. Each technic has its advantages and disadvantages. Briefly, the speed, simplicity, and transportability of the slide method are offset by the fact that not all spores can be distinguished microscopically (for practical purposes, this is limited to *Alternaria*, *Hormodendrum*, *Helminthosporium* and the rusts and smuts). The plate method may be criticized in failing to yield accurate volumetric figures and in the fact that not all spores will grow on culture media. Durham¹⁰²¹ has reviewed the various methods of sampling and counting spores, and has presented a table of the available information of spore counts for various cities in the United States, Alaska,

low level in December and January (FIG. 120). The same holds true for these molds in Boston, while *Aspergillus* and *Penicillium* have no seasonal incidence (Pratt¹⁰⁰⁹). Likewise in the Philadelphia area, while spores are present in appreciable quantities throughout the year, there is a major mold season from mid-May to mid-October, particularly for *Alternaria*, *Hormodendrum*, and smuts (Blumstein and McReynolds¹⁰²²). Spore showers were frequently observed. In San Antonio, Texas, Zink¹⁰²⁴ found the spores of *Alternaria*, *Hormodendrum*, and *Helminthosporium* to be present in the air throughout the year, with the first named showing peaks in July and December. On the basis of skin tests, the occurrence of constitutional reactions,¹ and the

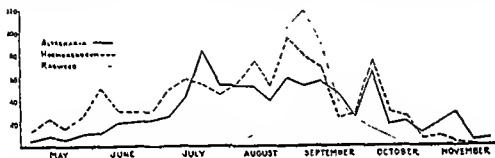


FIG. 120 SEASONAL INCIDENCE OF MOLD SPORES AND RAGWEED POLLEN IN SIXTY-THREE COMMUNITIES IN UNITED STATES AND CANADA DURING 1936 AND 1937

Graph represents weekly averages of daily slide counts of mold spores or pollen grains on area of 1.8 sq. cm. (Courtesy O. C. Durham and *Journal of Allergy*)

and some foreign countries. It would appear that nationally, in number and in widespread geographic distribution, the spores of *Alternaria*, *Hormodendrum*, and stem rust are predominant. The daily fluctuations in mold spore concentrations are more pronounced than those of pollen and are not as easily accounted for by weather conditions. "Showers" or "storms" occur on certain days, and can be recognized by data collected over large areas.

Mold surveys conducted by Feinberg and Little¹⁰⁰⁶ in Chicago and by Durham¹⁰²³ on a nation-wide scale have shown that some molds have distinct seasonal variations. Thus *Alternaria* and *Hormodendrum* spores begin to increase in number in May, reaching a peak in September and October, and returning to a

response to therapy, *Alternaria* was found to be the most important of the molds, with the other two less so; *Aspergillus* and *Penicillium* were thought to have little clinical significance. Observations by Harsh and Allen¹⁰²⁵ in San Diego, Calif., showed mold spores to be present throughout the year, with all genera exhibiting a wellmarked vernal peak. The types of major incidence included *Hormodendrum*, *Alternaria*, yeasts, *Penicillium*, *Macrosporium*, *Sporotrichum*, and *Helminthosporium*. In all, 27 genera and 131 species were identified, illustrating the complexity of this problem. In southern Michigan, *Alternaria* and *Monilia* are prevalent from May to November (Waldcott et al.¹⁰⁰⁴). In Milwaukee, *Alternaria* spores reach a maximum in early September, with secondary peaks in

¹⁰²¹ DURHAM, O. C. Publ No 17, Am Assoc Advancement Sc., pp 32-47, 1941

¹⁰²² Idem. *J. Allergy* 10: 40, 1938

¹⁰²³ BLUMSTEIN, G. I., and McREYNOLDS, S. U. *ibid* 15: 255, 1945

¹⁰²⁴ ZINK, P. L. *Ann Allergy* 2: 502, 1944

¹⁰²⁵ HARSH, G. F., and ALLEN, S. E. *J. Allergy* 16: 125, 1945

late July and early August, while *Hormodendrum* has its major peak in the early part of August, with minor peaks in June and October (Randolph and Squier¹⁰²⁶)

Durham¹⁰²² has pointed out the striking similarity of the quantitative geographic distribution of *Alternaria* and *Hormodendrum* to that of ragweed (Fig 121). The seasons for the mold spores vary from year to year in length and in regard to time of start and termination, such marked variations usually are

exception of rusts and smuts. Mold spores are given off into the air in enormous quantities, and, being very buoyant, are readily carried hundreds of miles. On the other hand, the average diameter of mold spores is from 3 to 5 microns, while the diameter of the common air borne pollen grains is from 15 to 50 microns. Moreover, as Wittich points out, mold spores disintegrate much less readily and their protein is much more slowly absorbed than that of pollen grains. All these points explain the

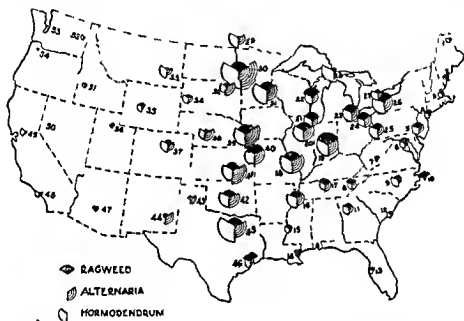


FIG 121 ATMOSPHERIC CONCENTRATION OF *ALTERNARIA* SPORES AND *HORMODENDRON* SPORES AS COMPARED TO THAT OF RAGWEED POLLEN, IN FIFTY THREE COMMUNITIES IN UNITED STATES AND CANADA

Area of each segment on map corresponds to total number of pollen grains or spore particles found in each locality in one season, or average of several seasons. (Courtesy O C Durham and *Journal of Allergy*)

not observed in the pollen seasons (Bernstein and Feinberg¹⁰²⁷). As an example of how local factors may influence the seasonal variations of molds, we may cite the observations of Harris¹⁰²⁸ that in Elyria, Ohio, the *Hormodendrum* count has two peaks (in June, and in October and November), coinciding with the two tomato crops in this region.

The total figures for *Alternaria* and *Hormodendrum* are not approached by those for any of the other air borne fungous spores, with the

fact that a given number of pollen grains will evoke more severe symptoms than will the same number of mold spores.

Mold allergy should be suspected, according to Hansen¹⁰²⁹ (1) if asthma or nasal symptoms are aggravated by damp, musty places (e.g., basements, woodsheds, old farmhouses, holds of ships, caverns) or in the vicinity of barns, hay lofts, straw piles, or grain threshing, if the symptoms are worse during damp rainy weather, and, if, on the other hand, the patients are better during the dry season and free from attacks during freezing weather or when the ground is covered with snow, all these

¹⁰²⁶ RANDOLPH T G and SQUIER T L. *WISCONSIN M J* 41: 538 1943

¹⁰²⁷ BERNSTEIN T B and FEINBERG S M. *J Allergy* 13: 231 1952

¹⁰²⁸ HARRIS I. H. discussion to Bernstein and Feinberg 1957

¹⁰²⁹ HANSEN K. *Deutsches Arch f Klin Med* 173: 469 1932

points are readily understood when one remembers that moisture, darkness, and warmth favor the growth of molds, (2) in patients with an unsatisfactory response to pollen therapy; (3) in patients whose symptoms do not appear to coincide with any known pollen count, (4) in patients who give no manifest response to cutaneous and nasal pollen tests, but whose asthma or rhinopathy is nevertheless seasonal. Blumstein⁹⁹ found that for some reason patients with seasonal respiratory mold allergy complained of little or no itching of the eyes, in marked contrast to those with pollinosis.

The diagnosis of mold allergy is tenable when the skin and mucous membrane tests coincide with the clinical history and both correspond with the sporulating period of the specific offending mold.

Individuals with hypersensitiveness to molds usually show an increase in symptoms during the summer months, particularly between the grass and the ragweed seasons, in most parts of the United States; a tendency to persistence of symptoms after the first frost; and, finally, complete freedom from symptoms during January and February. However, symptoms may also occur during the winter or at any time if the proper conditions are present; warm spells in the winter, for example, have been known to produce flurries of mold allergy symptoms. In environmental or occupational exposure, in sensitivity to nonseasonal fungi such as *Penicillium* or *Aspergillus*, in cases of extreme sensitivity, or when the patient has concomitant allergy to inhalants or foods, symptoms may be perennial. Some cases may be clinically free in mid-summer due to fluctuations in allergic equilibrium or to sensitivity to special varieties of fungi, and a few may present rhinopathy in the summer, and cough or asthma in the winter, possibly due to atmospheric factors or to bronchial infection (Feinberg¹⁰⁰). Mold-sensitive patients are not infrequently intolerant of yeast and yeast-containing foods, especially beer.

While the vast majority of mold patients have respiratory manifestations (seasonal or perennial allergic rhinopathy or asthma), Feinberg¹⁰⁰ reported a group of 13 cases of

seasonal neurodermatitis in whom the inhalation of fungous spores was convincingly demonstrated to be at least a part of the etiologic background.

Hyposensitization in mold allergy follows the same principles as in subcutaneous pollen therapy, injections being given once or twice a week depending on the time interval before the season starts. The extracts for treatment, as well as for skin testing, are prepared from the fungous spores only, the mycelia being excluded (Schonwald¹⁰¹). The usual initial dose is 0.05 cc. of a 1:10,000 dilution, and the maximum dose about 1 cc. of the 1:100 dilution or less. In a fair number of individuals the tendency to repeated systemic reactions makes it impossible to reach a high dosage. Three or four months of treatment usually suffice to bring about clinical control. Avoidance, as far as possible, of natural exposure to the allergen during the course of treatment makes for better results. It would appear that asthmatic symptoms are more readily controlled by such therapy than the rhinopathy. The tolerance achieved is nearly always only relative, symptoms usually following excessively high atmospheric spore concentrations. Since concurrent hypersensitiveness to pollens and other allergens is very frequently encountered, only by proper elimination of and/or hyposensitization to all pertinent allergens can successful treatment be achieved.

In the choice of fungi to be used in treatment reliance should be placed on positive skin reactions and on the number of spores in the air. When the patient reacts to two or more, mixtures are prepared depending largely on the second factor, since it is indicative of the degree of exposure. It is usually necessary to include *Alternaria* and *Hormodendrum*. If a number of *Aspergilli* produce reactions, either the greatest reactor or *Aspergillus fumigatus* or *flavus* is used. Others often found positive are *Penicillium*, *Chaetomium*, *Monilia*, *Trichoderma*, *Fusarium*, *Trichophyton*, *Phoma*, *Mucor*, and smuts.

¹⁰⁰ FEINBERG, S. M.: Arch. Dermat. & Syph. 40: 200, 1939.

¹⁰¹ SCHONWALD, F. Northwest Med. 40: 17, 1941.

2 SMUTS AND RUSTS

Cadham¹⁰³² was first (1924) to report asthma due to sensitization to grain rusts (3 cases). It is interesting to note, however, that Blackley, in his classic work on hay fever (1873), observed smuts on his slides and reported a spore count of *Ustilago segetum* of 7,000 per square centimeter



FIG 122 STINKING WHEAT SMUT (*Tilletia tritici*)
(X 500)
(Courtesy Dr F W Wittich)

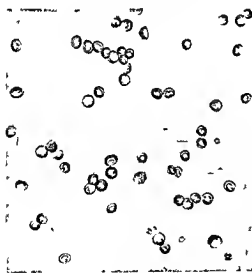


FIG 123 BARLEY SMUT (*Ustilago hordei*)
(Courtesy Dr F W Wittich)

Smut and rust are the parasitic fungi of the cereals. The most important smuts are those of wheat (*Tilletia tritici*, FIG 122, and *T. levis*), of corn (*U. maydis* and *U. zeae*), of oats (*U. avenae* and *U. levis*), and of barley (*U. hordei*) (FIG 123). The grain rusts (*Puccinia graminis*) (FIG 124) have not as yet been divided into subgroups

Wittich^{1033, 91} notably has called attention to the importance of these fungi in relation to asthma in workers in flour mills, in those living in the vicinity of such establishments and also of course, in farmers. This is easy to understand when one considers the fact that one single smutted wheat kernel may contain from 6,000,000 to 9,000,000 spores. Not only those engaged in this industry but in fact the entire population of the agricultural midwest and the Pacific northwest, where smuts and rusts are produced in incredibly vast quantities, are exposed to these fungi. During the season



FIG 124 WHEAT RUST (*Puccinia graminis tritici*)
(Courtesy Dr F W Wittich)

of 1935, according to Wittich and Stakman¹⁰³⁴ corn smut in certain areas reached a count of 1,000,000 spores per square foot in twenty-four hours. During the harvesting or threshing time in the wheat-growing district of the Palouse country in eastern Washington, as many as 5,000,000 spores may fall on each square foot of soil (Heald). According to the investigations made by Stakman during flights in an airplane, spores were present in the air at heights up to 16,000 feet. The spores are transported hundreds of miles by air currents—for example, from northern Texas to Minnesota within forty-eight hours (Wittich¹⁰³⁴).

While these figures for smut spore incidence are certainly impressive, it must be remembered that the smut spore granule is much smaller than the pollen granule; the volume of the smut spore is roughly one eighth that of

¹⁰³² CADHAM F T J A M A 83 27 1924

¹⁰³³ WITTICH F W Journal Lancet 59 382 1939

¹⁰³⁴ IDEM AND STAKMAN E C J Allergy 8 189 1937

pollen, so that actual contact is less than the figures might lead one to suppose.

Wittich¹⁰² has reported 8 cases, Harris¹⁰³ 13 cases, and Waldbott and Ascher¹⁰⁴ 7 cases of asthma in which the hypersensitiveness was attributable mainly to smut or rust spores. In these instances the identity of the causal agent was determined not by positive skin or conjunctival tests, but by the appearance of asthmatic attacks on experimental inhalation of spores, or on insufflation of the grain dust or the powdered smuts into the patient's nostrils. All these patients had their attacks between July and November; and all reacted favorably to hyposensitization with smut or rust extract. In workers exposed to grain mill dust, an extract of the dust gave satisfactory results.

In conclusion, it should be mentioned that all smut reactors also respond to tests with the corresponding dust (wheat dust, oat dust, etc.). On the basis of extensive exhaustion and cross reaction tests, Harris¹⁰³ adopted the view that wheat smut, for example, acting on wheat, may produce the wheat dust antigen, the oat smut, acting on oats, the oat dust antigen, etc. Furthermore, Wittich¹⁰² found that an individual hypersensitive to smut has a tendency to react to the host grain from which the smut originated.

E. CHEMICALS

Chemical substances act as inhalant allergens far more frequently than was formerly supposed. The difficulty arising in each of these cases is that of proving the existence of specific hypersensitiveness as against a non-specific irritation. It is a well-known fact, of course, that patients with asthma or rhinopathy—particularly those with the pathergic type—are prone to attacks following any kind of local irritation, due, for example, to insecticides, perfumes, and tobacco smoke. This type of reactivity is not to be considered here. The discussion will be confined to those cases in which the allergenic specificity of the chemical could be proved by strict avoidance as

well as exposure tests. Skin tests are almost entirely useless for this purpose.

This group includes the most varied inorganic and organic chemical compounds. Therefore, it is impossible to classify them from the chemical viewpoint, hence, we shall consider them in the approximate order of the frequency with which they act as allergic agents by inhalation.

The principal cause of asthma among furriers is a chemical used for dyeing furs—paraphenylenediamine, known in the trade as *ursol*. This chemical, when subjected to mild oxidation by the addition of a weak solution of hydrogen peroxide, forms a deep-black dye, quinone di-imine. The excess of the dyestuff rubbed off the pelts becomes pulverized; this dust is inhaled by the workers and thus may act as an allergen (Curschmann,⁴⁰ Mayer¹⁰⁵). Shilkret and Schwartz¹⁰⁶ were unable to confirm this explanation of the cause of asthma in fur workers. They found no one who reacted on skin testing with "fur dye dust" ("autogenous shop dust") who failed to react to stock house dust, nor could symptoms be reproduced by inhalation of the former (although two positive instances were obtained with aniline dye). They concluded that the active antigenic component of fur dye dust is not related to paraphenylenediamine or aniline dye or to their alteration products.

Asthma due to tar is observed mainly among asphalt workers and employees in tar plants. However, Thomas and Wicksten⁹⁹ reported a case of allergic purpura, hematuria, and albuminuria in a 16-year-old boy precipitated by the inhalation of tar fumes. Previous exposure had taken place by chewing tar in childhood. Patch tests with crude coal tar ointment were positive.

Another group includes specific hypersensitiveness to burning wood, charcoal, kerosene, and tobacco smoke. Duke⁹⁹ reported the case of a woman who was sensitized by the smell of charcoal burning beneath her window. Thereafter she was hypersensitive to open charcoal stoves. A case of respiratory allergy to the smoke of brown coal and another to kerosene have been observed by the senior author, the patients having been sensitized by

¹⁰² HARRIS, L. H. *J. Allergy* 10: 327, 1939

¹⁰⁴ WALDBOTT, G. L., and ASCHER, M. S. *Ann. Int. Med.* 14: 215, 1940

¹⁰³ HARRIS, L. H.: *J. Allergy* 10: 433, 1939

¹⁰⁵ MAYER, R. L. *Arch. f. Dermat. u. Syph.* 156: 311, 1928,

¹⁰⁶ SHILKRET, H. H., and SCHWARTZ, F. *J. Allergy* 14: 538, 1943

protracted inhalation Duke,¹⁰⁰ also Rappaport and Hecht,¹⁰¹ have described asthma in firemen that was produced by hypersensitivity to the smoke of wood. Vaughan²¹ mentioned the case of a farmer's wife who inhaled large amounts of smoke when the barn burned down. Thereafter she had attacks of asthma when wood fires were lighted in the fire place in her home. A scratch test with an extract of wood smoke (commercially prepared for the curing of ham) caused a severe anaphylactic shock. Biederman¹⁰² implicated the fumes of matches composed of red phosphorus and sesquisulfide of phosphorus as the cause of a case of asthma, but failed to present convincing evidence that this was on a specific allergic rather than a pathergic basis. Frugoni and Ancona¹⁰³ and Swineford¹⁰⁴ observed asthma actually produced by the fumes of burning 'asthma powders' (potassium nitrate, stramonium, swamp cabbage, lobelia) employed therapeutically. The sensitivity was shown to be to the last three ingredients. Hence in some cases symptoms may be prolonged by this measure.

Asthmatic attacks are not infrequently attributable to paradichlorobenzene, naphthalene, camphor and other insecticides. We do not refer here of course to insecticides of plant origin, such as pyrethrum.

Chronic acid vapor is known to be the cause of asthma in individuals working in chromium plating (Joules¹⁰⁵). Similarly, formaldehyde vapors can exert an allergenic effect. Specific hypersensitivity to sulfuric emanations in a sulfur spa was observed by the senior author.

Klauder, Miller, Vaughan, the present writers and others have observed, in physicians

and nurses, cases of asthma due to neoarsphenamine. An illustrative case is that of Vuletic. After two years of daily work with the drug he and his assistant developed first dermatitis of the hands followed by asthma. In addition, the latter also had generalized urticaria, mucohemorrhagic diarrhea and fever. Saunders⁷⁹ reported in himself the onset of profuse rhinorrhea and asthma from the inhalation of arsphenamine, neoarsphenamine, and mapharsen but not of tryparsamide. Scratch tests were positive and caused constitutional reactions, and while the patch test was negative, it evoked severe asthma 19 hours later presumably due to transepidermal penetration. In all these cases the allergen acted via the inhalation route, the attacks appearing while the individual was opening the ampules.

Feinberg and Watrous⁶² observed 14 cases of asthma and rhinopathy specifically due to the inhalation of the 'dust' of the synthetic chemicals chloramine T (chlorazene) and halazone used as water disinfectants in workers exposed to them. Contrary to the usual experience with hypersensitivity to chemicals, immediate whealing skin reactions were produced by direct testing and by passive transfer.

According to Zanger the ammonium persulfate that is added to flour is occasionally the causal agent in so called baker's asthma.

Griebel was able to demonstrate that a carpenter's asthma was provoked by a certain wood stain that contained iso amyl alcohol.

Rappaport and Hoffman¹⁰⁶ reported a case of urticaria due to inhalation of aliphatic non conjugated aldehydes, such as acrolein resulting from the oxidation of fats (glycerol in cigarettes oxidation of the fatty oils in the frying of foods) and to formaldehyde with which the patient was in occupational contact.

¹⁰⁰ RAPPAPORT B. Z. and HECHT R. J. A. M. A. 113: 104, 1919.

¹⁰¹ BIEDERMAN J. Ohio State M. J. 32: 236, 1936.

¹⁰² FRUGONI C. and ANCONA G. Pol. clinico (s. z. med.) 32: 161, 1925.

¹⁰³ SWINEFORD O. Jr. J. Allergy 8: 306, 1937.

¹⁰⁴ JOULES H. Lancet 2: 182, 1932.

¹⁰⁵ RAPPAPORT B. Z. and HOFFMAN M. M. J. A. M. A. 116: 2656, 1941.

CHAPTER XIV

INGESTANTS

THIS chapter will be devoted to a discussion of those substances taken by mouth—foods and drugs—that have been found to act as allergens not infrequently. The same substances can sometimes produce allergic symptoms by inhalation or contact, this, of course, is discussed in the relevant chapters. In principle there is no food or drug—whether of animal, vegetable, or inorganic origin—that cannot be an allergen.

A. FOODS

Foods can evoke almost all—including the most unusual—allergic manifestations. As might be expected, they are of predominant importance in causing allergic diseases of the gastro-intestinal tract, but they are also of great significance in allergic disorders of the skin, of the nervous system, especially migraine, and of the urinary tract, as well as in causing certain poorly understood systemic complaints. Foods are solely responsible for allergic conditions of the respiratory tract in only a few instances, although they may frequently act as adjuvant factors, as will be discussed below. Sensitivity to seasonal foods, such as berries, fruits, melons, and certain vegetables, may without careful evaluation of the case cause confusion with pollinosis or fungus allergy.

Reliable observations have implicated food allergy in the etiology of numerous instances of syndromes only rarely considered to be of this origin. Thus, the senior author¹⁰⁴⁶ has observed a fixed (FIG. 125) and even a bullous eruption of the skin, and of the mucous membranes of the mouth, due to lentils. Cooke¹⁰⁴⁷ has made similar observations of reactions attributable to ingestion of tomato. Another rare manifestation of hypersensitivity to food is fever, as described by Gay,¹⁰⁴⁸ Rowe, and others. Coca¹⁰⁴⁹ has observed that food allergies, detected by the specific tachycardia

method, can cause disturbances of the general peripheral circulation. Price¹⁰⁵⁰ pointed out the relationship of food allergy to arterial hypertension, especially from the cumulative effect of minor food allergens as regards the individual patient, and considered the kidney and vascular tree to constitute secondary shock organs in such cases, with the primary hypersensitivity resident in the gastro-intestinal tract. It is important that this mechanism be considered in determining the dietary regimen in cases of hypertension. According to Alvarez and Hinshaw,¹⁰⁵¹ food can at times produce mental depression, a feeling of "dopiness," and a number of curious sensations in the head. Unexplained and persisting fatigue or "fatigue unrelieved by rest" (Randolph⁷⁴⁶) may be due to foods. Such cases are almost always considered at first to be on a psychogenic basis and the symptoms do, indeed, strongly suggest neurasthenia. However, the condition is quite frequently associated with other allergic manifestations, particularly migraine, may show an unusual blood picture (Randolph and Gibson¹⁰⁵²), and will be relieved by prolonged elimination diet.

Table 30 presents a summary of the symptoms of alimentary allergies. This is only intended to indicate that any one of the symptoms listed can *occasionally* be elicited by some food. The reader is earnestly cautioned against the more or less general tendency to consider all such cases as due to food allergy. No such assumption is warranted.

Rinkel⁹⁷ has emphasized the fact that food sensitization may be either fixed and constant, or cyclic depending on cumulative responses according to the degree to which the food is included in the diet or eliminated therefrom. He divides food allergy into three clinical types: (1) the perennial, a primary food allergy; (2) the concomitant—clinically evident

¹⁰⁴⁶ PRICE, A. S. *Rev. Gastroenterol.* 10: 233, 1943.

¹⁰⁴⁷ ALVAREZ, W. C., and HINSHAW, H. C. *J. A. M. A.* 104: 2053, 1935.

¹⁰⁴⁸ RANDOLPH, T. G., and GIBSON, E. B. *Am. J. M. Sc.* 207: 638, 1944.

¹⁰⁴⁶ URNACH, E. *Klin. Wchschr.* 15, 1208, 1936.

¹⁰⁴⁷ COOKE, R. A., cited by Abramowitz and Russo ¹⁰⁴⁹

¹⁰⁴⁸ GAY, L. P. *J. Allergy* 4: 412, 1937.

¹⁰⁴⁹ COCA, A. F. *Ann. Allergy* 3: 101, 1945.

only while one inhales an allergen ragweed pollen for instance and highly specific and (3) the thermal which is either not at all evident or very mild unless the patient breathes cold air or is chilled at or below his critical level

The existence of an underlying food allergy requires unequivocal proof in every single case. This as explained in some detail on page 186 is best done by means of elimination diets, trial diets or propeptan diets in connection with careful daily food diaries. According to Coca⁷⁵⁴ the response of the cardiovascular system to ingestion of the allergenic food may

which are among the commonest food allergens are perhaps a bit more accurate than with other foods. It is probably safe to say that a patient giving a few positive skin reactions to foods is more likely to be food sensitive than one who gives a great many. Obviously a positive reaction to a food is in itself not an adequate indication for its elimination from the diet nor is a negative reaction proof of its innocuousness.

The reasons for the appearance of false positive reactions to skin tests have been discussed in detail on page 169. We shall therefore limit ourselves here to mentioning

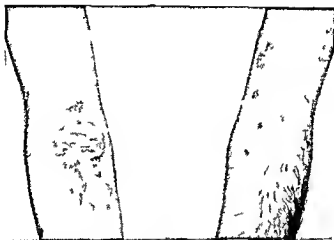


FIG. 125. FIXED EXANTHEM DUE TO HYPERSENSITIVENESS TO LENTILS.
In appearance lesions are indistinguishable from fixed drug eruption.

also be employed. The sudden appearance of a marked tachycardia or of hypotension suggests hypersensitivity to the particular food. Another approach consists in preprandial and postprandial leucocyte counts, a method introduced by Vaughan⁷⁵⁵ and called the leucopenic index. Skin tests—whatever the results may be—are not very reliable. Rinkel¹⁶³ states that 29 per cent of consistent nonreactors actually manifested symptoms after ingestion of an allergenic food while only 26 per cent of the constant skin reactors were actually afflicted with food allergy and only 24 per cent of the variable reactors proved to be allergic to some food. It would appear that skin tests with milk, egg and wheat

only the likeliest explanation—namely that the reaction is attributable to a past hypersensitivity that is no longer manifest clinically. The converse—false negative tests—can be explained on the basis of any of the possible reasons listed on page 170. It is best understood when one remembers that quite frequently the allergen is not the food stuff itself but its derivatives formed by the metabolic processes within the organism thereby producing secondary allergens (Urbach and Kitamura¹⁸³, Cooke¹⁸⁴, Stull and Hampton¹⁸⁵). For obvious reasons we are not as yet in a position to perform tests with these secondary allergens. However a means

¹⁸⁴ COOKE R. A. *Ann. Int. Med.* 16: 71, 1942.

¹⁸⁵ STULL A. and HAMPTON S. F. *J. Immunol.* 41: 143, 1941.

of accomplishing this in some cases may perhaps be suggested by the studies of Blamou-tier¹⁰⁴ on a patient who for about ten years had invariably had attacks of generalized

duodenal juice. But when specimens of the meat were incubated with both gastric and duodenal juice a positive skin reaction was obtained, and a passive transfer test with this

TABLE 30—Possible Clinical Manifestations of Food Allergy

GASTRO-INTESTINAL SYSTEM	NERVOUS SYSTEM
canker sores, aphthae	allergic headache
"indigestion"	migraine
pyrosis	epilepsy
flatulence	Ménière's syndrome
belching	vertigo
epigastric distress or pain	certain neuralgias
nausea	transitory aphasia and hemiplegia
vomiting	functional paralysis
intestinal cramps	amaurosis
abdominal pain	amblyopia
diarrhea	hypersomnia, insomnia
constipation	depression, mental dulness
mucous colitis	personality changes
spastic colon	
melena	CARDIOVASCULAR SYSTEM
pruritus ani	angina pectoris
	extrasystoles
RESPIRATORY SYSTEM	tachycardia
allergic rhinopathy	hypertension
bronchial asthma	hypotension
	hemorrhages (nasal, rectal)
CUTANEOUS SYSTEM	URINARY SYSTEM
dermatitis (eczema)	enuresis
neurodermatitis	bladder irritability
urticaria	renal colic
lichen urticatus	hematuria
angioneurotic edema	albuminuria
fixed pigmented erythema	
pruritus	MISCELLANEOUS
purpura	weakness
erythema multiforme	fatigue
acne vulgaris	irritability
	nervousness
	insomnia
	general aching
	yawning
	allergic toxemia
	fever

It must be strongly emphasized that most of these conditions are only very rarely due to food allergies.

urticaria and angioneurotic edema of the face five to six hours after eating lamb or mutton. All skin tests with lamb or mutton extract were negative, as were those with samples which had been incubated with gastric or with

liquid was likewise positive. Clearly the allergen was a product of the digestion of the meat, rather than the meat itself. Other important reasons for "false negative" skin tests to foods reside in the facts that the skin is often not concomitantly sensitized along with the shock structure and is therefore in-

¹⁰⁴ BLAMOUTIER, P.: *Presse méd.* 53: 162, 1945.

capable of reacting with the injected food protein extract, and that extracts of fruits and vegetables, as demonstrated by Tuft and his co workers, may, unless prepared and preserved by special technics contain little or none of the allergenic principle present in the fresh juice, probably due to enzymatic action.

Even food trials may be fallacious, because a hypersensitiveness may be related to only a certain kind of a given foodstuff or to a particular combination of a number of foods. Thus, Pagniez reported a case allergic only to strawberries grown in a certain Swiss canton. Vaughan¹⁰⁵⁷ observed a man who could tolerate celery grown in Florida, but not that grown in Colorado, and an analogous case manifesting allergic responses to Florida but not to California oranges. In Sticker's¹⁰⁶¹ case the allergic manifestations appeared after ingestion of honey from linden blossoms, while heather honey could be eaten with impunity. Balyeat¹⁰⁵⁸ has shown that sometimes apparent intolerance of milk may be due not to hypersensitiveness to the milk protein itself but rather to substances the animal has eaten in its feed, traces of which are contained in the milk. The situation is sometimes even more complicated than this—as in Duke's¹⁰⁶⁰ case in which asthmatic attacks followed ingestion of roasted and salted peanuts, whereas there was no response to peanuts that had been roasted and not salted, or to peanuts that had been salted and not roasted.

In occasional instances however, the specificity depends not only on the substance itself, but also on the method used in its preparation or on the combinations of foods eaten. Rowe⁷⁴⁰ observed cases of hypersensitiveness to fruit in which cooked fruit was not tolerated, while raw fruit was eaten with impunity—an observation which according to Adelsberger and Munter,¹⁰⁵⁹ is especially applicable to plums. Vaughan¹⁰⁶⁰ on the other hand, reported a case in which raw pears evoked allergic manifestations while cooked pears

did not. Withers¹⁰⁶¹ reported that about one fifth of his patients could tolerate certain cooked but not raw foods. This was most frequently true of cabbage apple and onion. One patient could take stewed apricots or figs, although the dried fruits produced asthma while another experienced rhinopathy after eating fresh corn but not corn meal. Similar observations have been made in regard to other foods including eggs and fish.

Particularly interesting are the cases in which only a given combination of foods but none of the ingredients individually acted as an allergen. Thus Duke reported on a patient who tolerated both raw and cooked eggs, but responded with allergic manifestations to traces of egg in cakes or cooked noodles and one of us observed a trained nurse who reacted with severe itching and papules to an omelet but was able to tolerate raw and cooked eggs milk and flour when these food items were taken separately. Similarly, Dekker described the case of a woman who had severe skin manifestations following ingestion of a pap composed of oatmeal and milk but who tolerated both milk and oatmeal perfectly when they were taken alone. Ratner mentioned two similar instances the first patient showed hypersensitiveness to chocolate and strawberries but would react only when both were eaten at the same time the second an individual hypersensitive to lobster and corn, suffered no reactions when one of these two items was eaten separately. There is also Funck's report on a migraine patient who tolerated butter eggs, and flour separately but had attacks on eating a combination of these items in the form of a pancake. Adelsberger and Munter¹⁰⁵⁹ made similar studies in several migraine patients one suffered attacks only after eating a combination of eggs (raw or cooked) plus tomato, another responded to mayonnaise, but not to eggs or oil taken individually. Finally, in rare cases a combination of a food and a drug may act as an allergen, for example, Fechner mentions fish plus phenobarbital or codeine.

Since, as discussed, the precise origin of the

¹⁰⁵⁷ VAUGHAN W. T. Discussion to Sulzberger M. B. and Simon F. A. J. Allergy 6: 55 1934

¹⁰⁵⁸ BALYEAT R. M. ibid 1: 516 1930

¹⁰⁵⁹ ADELSBERGER L. and MUNTER H. Alimentäre Allergie. In Samml. zwangl. Abhandl. d. Geb. der Verdauungs u. Stoffwechs. Krankh. vol. 12 no. 5 1934

¹⁰⁶⁰ VAUGHAN W. T. J. Allergy 1: 355 1930

¹⁰⁶¹ WITHERS O. R. Southern M. J. 30: 918 1937

food, the mode of preparation, and the combination of foods eaten are important factors in some cases, it is imperative that diet trials be made under conditions identical with those of the patient's exposure—that is, with the food or foods just as they were originally ingested by the patient.

Certain diagnostic difficulties also result from the fact that an allergic reaction often does not appear promptly after the test is made. Sometimes it fails to appear until twenty-four hours later (Laroche, Richet, and Saint-Girons,¹⁰⁶² Cooke,⁷⁶¹ Urbach²⁴⁹). Vaughan²¹ reported the case of a woman whose migraine attacks always set in precisely thirty-six hours after ingestion of chocolate. This makes it easy to understand why a nutritive urticaria, for example, does not always disappear promptly after one day's avoidance of the food that causes it. Pagniez and Coste¹⁰⁶² reported that a patient's urticaria reached its maximum as late as several days after ingestion of bread, and did not begin to decline until some twenty-four to forty-eight hours after the elimination of bread from the diet. And Rowe⁷¹⁰ has pointed out that, particularly in hypersensitiveness to fruit, the appearance of skin manifestations may sometimes be delayed for several days, and may persist despite thorough evacuation of the intestines.

When the reaction to a nutritive allergen is delayed for a number of hours, one of the following conclusions may be drawn. (1) the allergen is absorbed not in the upper part of the digestive tract but in the small or large intestine; (2) the allergen is not the unaltered food, but is either a product of digestion or a secondary antigen (produced, for example, by the influence of intestinal bacteria on the food protein). In the chapter on predisposing factors in allergy, we have attempted to explain the mechanism underlying those cases in which a food acquires allergenic properties only when a local predisposing condition, such as gastritis or colitis, coexists.

Evidence that the offending allergen is

present in the blood was obtained by Wingard.¹⁰⁶⁴ Patients with allergic dermatoses due to food hypersensitiveness were injected intracutaneously with their own serum drawn after the ingestion of the allergenic foods. Delayed skin reactions consisting of erythema and discrete papules were exhibited by 6 of 9 patients.

Furthermore, it sometimes happens that food hypersensitiveness appears only during the hay fever season. This has not as yet been adequately explained. There is a possibility that, as a result of a severe pollinosis, there is a general lowering of the threshold of tolerance, including that to the allergenic food.

The opposite problem—i.e., food allergy as a predisposing factor—is presented by Vaughan's²¹ patient who could eat strawberries and tomatoes with impunity as long as she avoided sunlight, exposure to sunlight, however, following ingestion of either, regularly brought on eruptions of the unprotected skin areas. Sunlight alone was tolerated perfectly. Similarly, Gougerot reported the appearance of an eczematous eruption of the face, the front of the chest, the forearms and hands (i.e., the areas exposed to the sun) following ingestion of a certain cheese. All these cases are examples of light hypersensitiveness in which nutritive allergy is the predisposing factor.

Paul Gross¹⁰⁶⁵ observed a sudden onset of what appeared to be a physical urticaria in his 2-year-old son when the child was taken out for a walk in cold weather, urticarial wheals appeared on the uncovered areas of his skin. This was found to be due to a certain brand of gelatin dessert; when he was given another type, he could be exposed to cold without effect, but the urticaria recurred as soon as the first gelatin dessert was deliberately reinstated. In this case, the food allergy predisposed to hypersensitiveness to a physical agent—cold.

Determination and elimination of the predisposing nutritive allergens is imperative in such cases, as a requisite to the management of the hypersensitiveness to the second antigen (e.g., cold, light).

¹⁰⁶² LAROCHE, G., RICHEL, C., JR., and SAINT-GIRONS, F. *Paris méd* 13 450, 1914.

¹⁰⁶³ PAGNIEZ, P., and COSTE, F. *Bull et mem Soc med d hôp de Paris* 48: 1365, 1924.

¹⁰⁶⁴ WINGARD, R. M.: *Arch. Pediat* 60 139, 1943.

¹⁰⁶⁵ GROSS, P. personal communication.

It must be remembered, furthermore, that a case of hypersensitiveness to a food may present a quantitative problem. Thus, many patients can tolerate an allergen—egg or milk, for example—when taken in small quantities for a day or two, though allergic symptoms will be elicited within the next few days by the cumulative effect of the allergen. Another common observation is that small quantities of chocolate may be tolerated, whereas larger amounts will, for example, evoke migraine.

The fact that foods of both animal and vegetable origin may act as inhalants, producing respiratory allergies, infantile dermatitis, and other clinical pictures was discussed in the last chapter. However it is important to realize that unless this possibility is kept in mind patients extremely hypersensitive to foods will continue to have symptoms from foods which they never ingest. Sensitivity to food odors is very easily overlooked.

Likewise, numerous observations regarding food as contactants will be included in a subsequent chapter. But it must be pointed out that the same food may act by both ingestion and epidermal contact in the same individual, producing either the same or unrelated clinical manifestations. Pertinent examples include the following cases: neurodermatitis of the face, arms, and cubital and popliteal spaces due to the ingestion of egg, and superficial dermatitis due to contact with egg white (Templeton¹⁵⁹), neurodermatitis of the flexures and neck due to ingestion of wheat, and contact dermatitis of the hands and face due to handling wheat flour (Templeton¹⁵⁹), papular skin rash and severe asthma due to ingestion of milk and wheat, and dermatitis of the exposed areas on contact with casein and wheat flour in a sausage maker (Deissler¹⁶⁰), dermatitis of the hands due to eating tomatoes, or from peeling or slicing tomatoes (Rowe¹⁶¹), papular urticaria due to ingestion of lemon, and a vesicular reaction to contact with lemon (Urbach¹⁶²), swelling of the face around the eyes almost immediately after the ingestion of eggs, and swelling and blotching of the face at the site of contact promptly after application of egg or egg shells and lasting for an

hour (Mauser¹⁶³), a pastry cook with dermatitis from external contact with eggs as well as from ingestion and similar instances due to lettuce in salad makers, and to tomatoes and fish in workers exposed to these foods (Downing^{167b}).

According to Ratner^{167c} the modes of acquisition of food allergy in childhood are (1) sensitization in intra uterine life to undigested food proteins that enter the blood stream of the mother and gain access to the fetal circulation through the placental membrane (2) sensitization via breast milk (3) occasional feeding of raw milk during the neonatal period, (4) taking of raw foods during convalescence from disease, (5) overfeeding (6) fad diets or excessive indulgence in seasonal or bizarre foods. In the case of adults, of course only points 4 to 6 are operative, furthermore, allergization may occur at any age as the result of diseases of the gastro-intestinal tract and during states of lowered bodily resistance and emotional stress. Particularly important in this regard are acute infectious diseases, such as influenza, measles, and pertussis.

Finally the management of nutritive allergies should be briefly considered here. It must be said at once that subcutaneous hypo-sensitization methods are entirely futile and even dangerous. Moreover, avoidance of an allergenic food is feasible only if the food is not a common one. When the causal agent is known to be a common and important food—e.g., egg, milk, or bread—two oral methods are of value: (1) oral hyposensitization and (2) deallergization by means of specific propeptans. As shown in detail below the former consists of administration of minute quantities of the allergen suspended in water and given daily in doses that are slowly and gradually increased every second day, the course of treatment is continued until tolerance to a normal amount of food is acquired. The success of this method depends largely on the cooperation of the person responsible for its conduct, and thus to a considerable extent on the clarity of the instructions given by the physician. A detailed list of the foods containing the allergen in question should be

^{159a} DEISSLER, K. J. cited by Templeton¹⁵⁹

¹⁶¹ ROWE, A. H. cited by Templeton¹⁵⁹

¹⁶² URBACH, E. cited by Templeton¹⁵⁹

¹⁶³ MAUSER, C. L. cited by Templeton¹⁵⁹

^{167b} DOWNING, J. C. discuss on to Templeton¹⁵⁹

^{167c} RATNER, B. J. *Ped* at 16: 653, 1940

supplied. Complete elimination of the allergen is essential, from the inception of the treatment until its completion. A fresh solution should be prepared daily. If a reaction occurs, one reverts to a weaker dilution and then proceeds from that point according to the original schedule. After successful hyposensitization, the patient should make it a point to eat some of the particular food every day for several months. This method was successfully employed by Kesten, Waters, and Hopkins,⁷³⁴ and more recently by Edwards¹⁰⁷² (Table 31).

The propeptan treatment personally preferred by the writers has been described in detail (p. 220).

¹⁰⁷² EDWARDS, H. E. *Canad. M. A. J.* 43: 234, 1940

Aside from these specific methods of treatment, special attention must also be given to the predisposing factors, particularly to conditions of the gastro-intestinal tract. As has been shown in some detail on page 61, an existing hypo- or acidity must be combated not only by means of a suitable dietary regime, but also with large doses of hydrochloric acid and pepsin. When a lowered serum enzyme level gives evidence of pancreatic hypofunction, administration of pancreatic enzyme preparations is indicated. The intestinal tract merits most particular attention. Diseases of the small and the large intestine, including constipation, must be corrected with appropriate diets. Laxatives are to be avoided as far as possible. The bacterial flora of the intestines must be closely

TABLE 31—Technic of Oral Hyposensitization

DIRECTIONS. Each dose should be freshly prepared and taken once daily for two successive days. If any subjective or objective symptoms are noticed, the dose should be decreased and not increased until it is well tolerated.

Milk.

Directions. Mix the measured amount of milk in the indicated quantity of water.

Day	Milk	Water	Dose	
			Mixture	Milk (Undiluted)
1, 2	1 drop	1 qt.	1 tsp	
3, 4	2 drops	1 qt	1 tsp	
5, 6	4 drops	1 qt	1 tsp	
7, 8	8 drops	1 qt	1 tsp	
9, 10	16 drops	1 qt	1 tsp	
11, 12	16 drops	1 qt	2 tsp	
13, 14	16 drops	1 qt	2 tbsp	
15, 16	16 drops	1 pt	2 tbsp	
17, 18	16 drops	$\frac{1}{2}$ pt	2 tbsp	
19, 20	16 drops	$\frac{1}{4}$ pt	2 tbsp	
21, 22	16 drops	$\frac{3}{8}$ pt	2 tbsp	
23, 24	$\frac{1}{2}$ tsp.	1 tbsp	1 tsp	
25, 26	$\frac{1}{2}$ tsp	1 tsp	1 tsp	
27				$\frac{3}{8}$ tsp
28				1 tsp
29				2 tsp
30				1 tbsp.
31				2 tbsp
32				3 tbsp.
33				$\frac{1}{4}$ cup
34				$\frac{1}{2}$ cup
35				1 cup
36				1 glass
Thereafter, daily—				1 glass (at least)

TABLE 31—*Concluded*

EGG

Directions Hard boil an egg cut it in half and discard the yolk. To obtain the smallest feasible port on continue to halve the portions of egg white progressively into pieces of $\frac{1}{4}$ $\frac{1}{8}$ $\frac{1}{16}$ $\frac{1}{32}$ $\frac{1}{64}$ and $\frac{1}{128}$

Day	Dose	
	Egg White	Whole Egg
1 2	$\frac{1}{128}$	
3 4	$\frac{1}{64}$	
5 6	$\frac{1}{32}$	
7 8	$\frac{1}{16}$	
9 10	$\frac{1}{8}$	
11 12	$\frac{1}{4}$	
13 14	$\frac{1}{2}$	
15 16	1	
17 18	1	
19 20	1	
21 22	1	
23 24	1	
25 26	1	
27 28	1	
Thereafter daily		1 (at least)

WHEAT

Directions Mix the measured amount of flour in the indicated quantity of water. The dose should be added to soup, milk, or other suitable food.

Day	Flour (Whole Wheat)	Water	Dose	
			Mixture	Whole Wheat
1 2	$\frac{1}{4}$ level tsp	1 tbsp	$\frac{1}{2}$ tsp	
3 4	$\frac{1}{4}$ tsp	1 tbsp	1 tsp	
5 6	$\frac{1}{4}$ tsp	1 tbsp	2 tsp	
7 8	$\frac{1}{2}$ tsp	1 tbsp	all	
9 10	$\frac{3}{4}$ tsp	2 tbsp		
11 12	1 tsp	2 tbsp		
13 14	2 tsp	$\frac{1}{4}$ cup		
15 16	1 tbsp	$\frac{1}{4}$ cup		
17 18	2 tbsp	$\frac{1}{2}$ cup		
19 20				$\frac{1}{4}$ slice of bread
21 22				1 slice of bread
23 24				2 slices of bread
Thereafter daily				bread and cereal

watched and must be dealt with, when necessary, by means of *Bacillus acidophilus* and *B. coli* preparations.

Holmes⁹⁰ reported excellent results in the treatment of various food allergies by means of vitamin C (500 mg daily for one week).

The writers and others have had no success at all with this method.

It is quite impossible to give anything like a complete list of all the foods that have at one time or other acted as allergens. We

shall have to content ourselves with mentioning only the more important ones, and must refer the reader to Rowe¹⁰⁰ and Hanhart¹⁰⁷³ for a more detailed treatment of the subject.

Vaughan¹⁰⁶⁰ attempted to establish a biologic classification of the foods of vegetable origin; Ellis⁹⁷⁴ has done the same with respect to foods of animal origin. They suggested that clinical hypersensitiveness would occur in accordance with this grouping. However, statistical analyses, made by Withers, Ratner, Piness, and others, of the occurrence of positive skin tests in relation to botanically or biologically related foods, have not borne out this assumption.

1. FOODS OF ANIMAL ORIGIN

Egg is probably the most common allergizing agent in this category. It is most active in the form of raw egg white. In fact, the intolerance is occasionally restricted to this form, though it generally embraces cooked egg white as well. It is only in very exceptional cases that the allergenic action is restricted to cooked egg white and is not manifested in relation to the raw substance. From the allergic viewpoint, ovalbumin is the leading protein fraction in egg white. There is far less frequent hypersensitiveness to egg yolk alone (Castaigne and Chiray), but here, too, the allergenic action may be restricted to either the raw or the cooked substance (Pariot and Simonin). In contrast to many other food allergens, egg white produces symptoms very rapidly.

Hypersensitiveness to egg white is of particular significance because mere traces of the substance are capable at times of eliciting manifestations of the greatest severity. The writers have observed the case of a boy who had urticarial swelling of the buccal mucosa, vomiting, and diarrhea whenever he cut his bread with a knife that had previously been used on an egg. Both Sutton and Dekker have reported anaphylactic symptoms provoked by mere presence of the patient in a room in which an egg was being opened. It is not difficult to understand, in view of such observations, how a very hypersensitive nursing

infant may respond with allergic manifestations to its mother's milk when the mother has previously eaten eggs (Donnelly,¹⁵⁹ Moro; Gyorgy).

Egg appears to cause cutaneous manifestations more frequently than other symptoms. In the section on infantile dermatitis, the significance of positive reactions to egg white in this disease will be discussed in detail. Neurodermatitis, urticaria, and angioneurotic edema (Fig. 126) are frequently produced by egg; vomiting, diarrhea, rhinopathy, and asthma, as well as other clinical manifestations,



FIG 126 ANGIONEUROTIC EDEMA DUE TO HYPERSENSITIVENESS TO EGGS

may also be elicited, though these occur less often. It is, therefore, most important to know just what dishes are prepared with eggs and are likely to contain some traces of egg; for, as mentioned, the minutest quantities suffice to evoke severe reactions in hypersensitive individuals. In this connection, mayonnaise, salad dressings, cream sauces, ovalette and ovine (an egg powder) must be borne in mind as common causes of reactions. Furthermore, it must be remembered that most cakes, custards, puddings, and muffins, unless specially prepared, contain egg white, and that it is also to be found in some baking powders,

¹⁰⁷³ HANHART, E.: Deutsche med. Wchnschr. 63: 1753, 1937.

⁹⁷⁴ ELLIS, R. V.: J. Allergy 2: 246, 1931.

some sauces, some prepared cake and pan cake flours, almond cakes, waffles, many kinds of candies, ice creams sherbets, icings garnishes, breading, croquettes, stuffings macaroni, noodles, dumplings, and even in some sausages. The glazed crust on rolls pretzels, and some breads is produced with egg white.

An egg free diet will be found on p. 190.

The increasing use of viral and rickettsial vaccines prepared on chick embryonic tissue or egg yolk, such as certain typhus, yellow fever influenza, Rocky Mountain spotted fever, and equino encephalomyelitis vaccines has led to a number of reports of severe constitutional reactions following their injection in egg sensitive individuals. Roth^{167a} described 32 cases requiring hospitalization after typhus immunization, of which 23 were of the 'foreign protein' type with fever, chills, malaise, absence of blood eosinophilia, delayed onset of symptoms, and without personal or family history of allergy, and 9 were allergic, attributed to residual traces of egg antigen in the vaccine. The latter exhibited gastro intestinal symptoms, urticaria, asthma, and mixed syndromes, and were characterized by lack of fever, immediate and explosive onset, eosinophilia, and previous personal and family histories of allergy. Four were definitely known to react to ingestion of egg. There were no deaths. Raynolds¹⁶⁸ saw two similar cases, and Lieder^{167b} one, as well as another due to equino encephalitis vaccine. Severe constitutional reactions were observed by Swartz^{167c} after an injection of yellow fever vaccine, and by Sprague and Barnard^{167d} after typhus and yellow fever vaccines. In Rubin's^{167e} case of angioneurotic edema following inoculation with these preparations, the sensitivity was demonstrably due to egg yolk, rather than the white. Sulzberger and Ascher^{167f} reported three cases of urticarial and erythema multiforme like eruptions along

with symptoms resembling those of serum sickness following injections of yellow fever vaccine. Forman¹⁶⁸ mentioned a fatal reaction in a known egg sensitive child in about fifteen minutes after Rocky Mountain spotted fever vaccine was given. The general incidence of reactions to chick embryo or yolk sac tissue vaccines appears to be low. Careful questioning regarding existing sensitivity and preliminary skin testing with egg and chicken meat antigen would be of value in detecting potential reactors.

Milk is second in order of frequency among the allergizing foodstuffs of animal origin. As is true in the case of egg hypersensitivity to milk is encountered more frequently among infants and young children than among adults. While the majority of patients are affected only by raw and pasteurized milk, others are allergic to heated milk as well. Ratner and Gruel have shown that the loss of antigenic properties in boiled milk is due to the coagulation of the whey proteins. The degree of hypersensitivity may be so extreme that swelling of the tongue and lips is seen to result from drinking one drop of milk diluted with water (Schloss). Such observations help to explain why many individuals who are allergic to milk also respond with symptoms to butter—which is known to contain only a very low percentage of protein.

While milk contains four proteins, only the lactalbumin and, far less frequently, the casein are of importance in this connection. When the hypersensitivity is specifically to the lactalbumin, the patient who cannot tolerate cow's milk can drink goat's or sheep's milk with impunity. But this is not the case in instances of hypersensitivity to casein, for, as Wells¹⁶⁹ has shown, casein from the milk of an animal of any given species shows a closer biologic relationship to the casein of another species than it does to the whey proteins. Since cow's milk contains about seven times as much casein as lactalbumin, cases sensitive only to the latter may fail to react to the usual test extracts, but will react to lactalbumin extract or to tests with whole pasteurized milk. The tendency on the part of some pediatricians to discount casein as a

^{167a} ROTH V. E. Bull. U. S. Army M. Dept. No. 88 p. 111 May 1943.

^{167b} RAYNOLDS A. H. J. A. M. A. 128 613 1945.

^{167c} LIEDER L. E. Letters Internat. Corr. Club of Allergy Series 8 58 1945.

^{167d} SWARTZ H. F. J. Lab. & Clin. Med. 28 1663 1943.

^{167e} SPRAGUE H. B. and BARNARD J. R. U. S. Nav. M. Bull. 45 71 1945.

^{167f} RUBIN S. S. J. Allergy 17 21 1945.

¹⁶⁸ SULZBERGER M. B. and ASCHER C. U. S. Nav. M. Bull. 40 411 1942.

¹⁶⁹ FORMAN J. Letters Internat. Corr. Club of Allergy Series 8 83 1945.

cause of allergic manifestations is rebutted by a report by Cooke,¹⁰⁵¹ among others, of a case of nasal allergy due to ingestion of casein.

Although it is true that almost all reports refer to hypersensitiveness to cow's, sheep's, goat's, or mare's milk—therefore usually appearing after the infant has been weaned—there have been a few reports of hypersensitiveness exclusively to human milk (Richet¹⁰⁵²). In such cases, however, appropriate control tests must always be performed to confirm the assumption that the hypersensitiveness is to the mother's milk itself; for there is always a possibility that the infant may be allergic to some food or drug ingested by the mother, traces of which are secreted into the milk. In this connection it is interesting to note Balyeat's¹⁰⁵³ observation that a child allergic to wheat gave an eczematoid response to cow's milk only when it came from cows that had been fed with bran; milk from animals on green fodder was tolerated perfectly. Dice¹⁰⁵⁴ has shown that onion flavor appears in cow's milk four to five minutes after being ingested and persists for five to six hours. Cazott observed a patient with asthma due to cottonseed contained in the milk of a cow fed with cottonseed meal, provided large quantities of the milk were taken.

The clinical manifestations of the reactions to milk can run the entire gamut of typical phenomena—and may also include atypical manifestations. To mention one example of an unusual reaction to milk, Rubin¹⁰⁵⁵ reported 4 instances of allergic melena in newborn infants. McLeond and Jaeger¹⁰⁵⁶ point out that milk intolerance is a more common cause of unrecognized disturbances in children than usually considered. Although skin tests were negative, in many children various abdominal complaints, pallor, lassitude, irritability, restlessness, repeated colds, asthmatic bronchitis, and enuresis were shown by clinical tests to be due to milk, and could be controlled by its elimination from the diet.

An unusual case of milk sensitivity in a nurse was reported by Randolph¹⁰⁵⁷ and re-

vealed that milk may be responsible not only for allergic headache of the migraine type, but also for alterations in consciousness and incapacitating fatigue between the frank attacks. Elimination diets pursued for an inadequate period were misleading. As is so often the case, skin tests were negative, even though in this instance, constitutional and focal reactions were precipitated. Symptoms were also elicited by the odor of milk while working in a formula kitchen and while feeding infants, and erythema of the skin by contact with regurgitated milk.

Just as has been said of eggs, milk is to be found in any number of foods in which its presence would not be suspected by the uninitiated. Thus, many kinds of bread, particularly the better grades of white bread, are made with milk, it is also included in the preparation of cakes, cookies, custards, ice creams, macaroni, noodles, spaghetti, cream soups and sauces, commercial salad dressings, oleomargarine, candies, malted milk, milk chocolate, and Nestlé's and other infant foods.

A milk-free diet will be found on p 189

Individuals who are hypersensitive to the lactalbumin of milk cannot tolerate cheese prepared from whey, such as cottage cheese, cream cheese, or Gervais. In the processing of many varieties of cheese, lactalbumin is largely removed or so denatured as to be eaten by many milk-sensitive patients without difficulty. However, in view of the many factors involved, a food trial should be performed before a particular type is added to the patient's diet. Individuals allergic to casein, on the other hand, react to cheeses that consist primarily of casein or the curd fraction—e.g., American cheese, Edam, Gorgonzola, Parmesan, Roquefort, and Swiss. In occasional instances, however, the hypersensitiveness is not a reaction to the milk protein in the cheese but to the molds that ripen it, especially in the case of the Camembert and Roquefort varieties.

Therapeutic injections of milk or milk derivatives, while no longer widely employed, are notoriously capable of giving rise to severe systemic reactions in sensitized individuals. The senior author recently saw a physician who was given injections of milk for the treatment of keratitis. The second injection

¹⁰⁵¹ COOKE, R. A. New York State J Med 43: 1125, 1943

¹⁰⁵² RICHEL, C. cited by Laroche, Richet, and Saint Girons 1902

¹⁰⁵³ DICE, J. R. North Dakota Statist Monthly Bull 6: 6 (Nov. 4), 1944

¹⁰⁵⁴ RUBIN, M. L. Am J M Sc 200: 353, 1940

¹⁰⁵⁵ McLEOND, P. A., and JAEGER, D. S. Southern M J 36: 571, 1943

caused a nearly fatal shock. Incidentally, the keratitis healed, but recurred several months later.

The next important group of ingestants embraces *fish* and *seafood*. Hypersensitiveness to all kinds of fish is very rare, it is usually confined to one or more species. Group relationships exist but have not been adequately investigated. Every species of fish can, in principle, be responsible for allergy. The specificity is so great in some occasional cases that the patient will react only to Norwegian sardines, for example, and not to any other (De Besche). As a rule the reactions appear very promptly as urticaria, angioneurotic edema, dermatitis (FIG 127), gastro intestinal disorders, and even asthma. Unfortunately,

Ratner, Balyeat and Bowen) Hypersensitiveness to fish is sometimes so extreme that severe anaphylactic manifestations may be provoked by the mere odor (see p 242).

Mention must also be made here of other seafoods that frequently act as allergens, such as mussels, oysters, lobsters, crayfish, shrimps, and crabs.

Finally, all kinds of *meats* come into consideration as potential nutritive allergens: pork first and foremost, then beef, veal, lamb, mutton, rabbit, chicken, turkey, duck, goose, as well as the various game foods. De Besche reports attacks of asthma attributable to horse meat in Europe. In this connection Kopaczewski's and Roux's independent observations, in Poland and France, respectively,

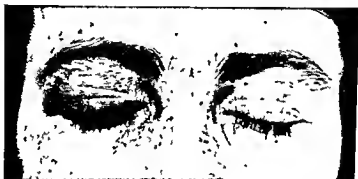


FIG 127 ACUTE DERMATITIS WITH SWELLING OF EYELID DUE TO HYPERSENSITIVENESS TO FISH

skin tests cannot be depended upon. It is not always easy, in a given case, to decide whether there is a nutritive allergy or whether some toxic by products may not have been formed (by improper refrigeration, for example). Strangely enough, the hypersensitiveness quite often relates only to cooked fish—as for example, in Kuestner's famous case that led to the discovery of the Prausnitz-Kuestner reaction. This explains why caviar (raw sturgeon roe) may sometimes be eaten with impunity by an individual who is hypersensitive to cooked sturgeon.

Minute traces of fish protein often suffice to provoke symptoms—as, for example, the infinitesimal particles of fish skin commonly used to clear coffee in Norway (De Besche), and similarly used to clear cheap white wine in France—not to forget the traces of protein remaining in cod liver oil (Hoffman and

that a higher percentage of primary reactions following injections of horse serum is found among individuals who regularly eat horse meat than among those who eat other varieties of meat, seem worthy of special attention. On the other hand, Hansen reported a fatal allergic reaction in a child who ate horse meat several weeks after an injection of horse serum. Sausage, ham, and other prepared meats deserve special mention as nutritive allergens, although it is true of course that the causal agent is not always the animal protein itself, but occasionally the salt, pepper, spices, or salt peter that has been added, or intermediary products resulting from the smoking process. Some of the hypersensitivities to lard, goose fat, and similar shortenings are attributable to traces of the particular meat protein remaining in the fat, in which case the allergic manifestations disappear on preadministra-

tion of the corresponding propeptans; but a few of these patients can be proved to be allergic to the fat itself. Individuals hypersensitive to pork, therefore, cannot eat pies, for example, that have been prepared with a shortening consisting of hog lard. Certain common sources of error should be pointed out



FIG 128 SUBACUTE DERMATITIS IN CHILD OF SEVENTEEN MONTHS, DUE TO HYPERSENSITIVENESS TO VEAL

here: nearly all canned soups, including vegetable and chicken soups, contain beef, as does also certain gelatins. Veal is frequently used as a substitute in chicken salad.

It is noteworthy that in cases of hypersensitivity to the meat of a certain animal, the liver, sweetbread, kidney, and brain of the animal can be eaten with impunity. The contrary has also been observed. Thus, Harten reported a case of severe asthma following ingestion of lamb, beef, and chicken livers, while the meats of these animals were well

tolerated. This hypersensitivity, in other words, was organ-specific and not species-specific.

Group sensitivity is not very common, as a rule the hypersensitivity is in relation to one or two of the meats most frequently eaten. The writers have frequently observed that individuals allergic to beef, could tolerate veal and vice versa. Meats are not infrequently responsible cutaneous manifestations (Figs. 128, 129). In rare instances, unusual clinical pictures may be traced to animal protein, as illustrated in FIGURE 130.

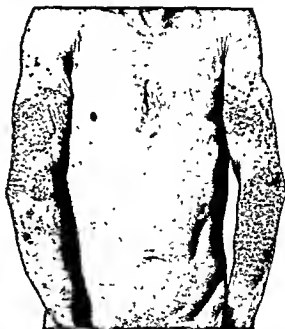


FIG 129 CHRONIC DERMATITIS DUE TO HYPERSENSITIVENESS TO BEEF

2 FOODS OF PLANT ORIGIN

While, in the light of our present knowledge, the allergenic factors in foods of animal origin are almost exclusively proteins, it has been proved that a number of substances (proteins, carbohydrates, fats, salts, acids, or spices) can be the active agents in cases of hypersensitivity to vegetable foodstuffs. Further investigation will be required to determine whether or not allergenic action can also be exerted by other chemical substances of nonprotein nature but specific for the particular plant. Thus, Schoenhof claimed to have demonstrated such an allergen in asparagus, and W. Jadassohn and Zaruski in celery. The hypersensitivity is occasionally

a reaction to added substances as for example the green coloring matter used for staining gelatin. This dye contains 2.6 per cent of aniline color (Baer¹⁹³⁵).

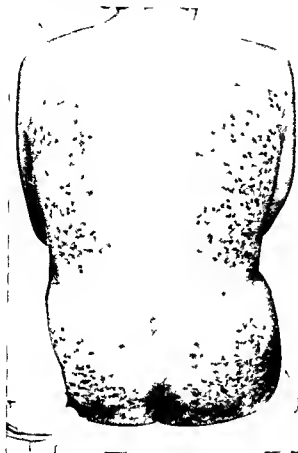


FIG. 130 HEMORRHAGIC EXANTHEM DUE TO HYPERSENSITIVENESS TO RYE.

a) CEREALS

Almost all authorities agree that hypersensitivity to *wheat flour* is among the most common of all nutritive allergies. This is readily explained by the fact that flour is eaten with almost every meal. For wheat flour is a constituent not only of bread, macaroni, spaghetti, noodles, cakes, pastries and pies but also of gravies, soups, cream sauces, sausages and coffee substitutes. Wheat is also found in many other food products such as infant foods, prepared flours and proprietary breakfast cereals. The commercial trade

names are never to be taken too literally for certain brands of corn flour, buckwheat flour, rye bread and even pumpnickel contain wheat flour. Gluten, a preparation for diabetes, also contains wheat. Ralston Rye Krisp is a product that can be depended upon as being free from wheat, egg or milk.

A wheat-free diet will be found on p. 191.

We have observed a number of cases in which the hypersensitivity to wheat was specific—i.e. in which rye, corn and other cereals were tolerated. Occasional instances of group hypersensitivity to many or all flours are also encountered of course.

Hypersensitivity to rye occurs more frequently in Europe than in America owing to the simple fact that in general rye is eaten far more extensively there. It is interesting to note the observation reported by Benjamins and by Gutmann that hay fever patients with hypersensitivity to rye pollen respond to the ingestion of rye bread with hay fever manifestations which disappear when it is eliminated from the diet and reappear when it is again eaten.

Corn is a not uncommon cause of allergy. While corn flour is not generally much used in bread, it is extensively eaten in the form of corn meal or as hominy, polenta, etc. The avoidance of corn when indicated is quite difficult since corn or corn syrup is probably combined in more prepared foods than any other single foodstuff. Aside from its inclusion in many breakfast cereals, salad oils (such as Mazola), corn meal and cornstarch, this food must be looked for in any of the following: almost all commercial candies, chewing gums, marshmallows, many sausages, hams and bacon, almost all canned fruits and some frozen fruits, many breads and pastries, most ice creams, ices and sherbets, baking powder, prepared desserts including gelatins, Bourbon and other whiskeys, carbonated beverages and some tomato soups and catsups. Popcorn may act as both an ingested and inhaled. Cornstarch is widely employed as a dessert and as a thickening for soups, gravies and sauces.

Barley is utilized in children's foods, coffee substitutes, soups and above all in the manufacture of malt and beer. Oats are widely eaten in the form of oatmeal, particularly as a

breakfast food, but also in prepared crackers and wafers. *Rice* is rarely an offender.

Mention must be made here of other plants that, although not included among the cereals from the botanic point of view, are used either alone, or more frequently in combination with wheat, corn, and other flour, in the preparation of bread, cakes, and proprietary food products.

Buckwheat allergy is relatively rare, but can be extraordinarily severe. It is advisable, therefore, to be cautious in carrying out skin tests with buckwheat.

Hypersensitiveness to *flaxseed* cereal must also be mentioned here. Flaxseed is present in Roman Meal and in Uncle Sam's Health Food. Vaughan has reported the case of a woman who was so allergic to flaxseed that she responded with angioneurotic edema of the tongue and of the mucosa of the mouth to the first mouthful of flaxseed cereal. Bowen and Walzer observed manifestations of flaxseed allergy brought on by drinking milk from cows that had been fed flaxseed meal.

Cottonseed flour is occasionally contained in human foods, especially bakery products and cereals, and is sometimes used in the manufacture of gin. Simon¹⁰⁵⁷ has described three pertinent cases of asthma along with burning and itching of the mouth and swelling of the lips following ingestion of cookies probably made with this substance. He feels that the water-soluble fraction exceeds the oil in importance. As mentioned elsewhere, appreciable quantities of cottonseed may appear in cow's milk if it is included in the animal's feed. The widespread use of cottonseed oil will be considered below.

Finally, there is *soy bean flour*, which is being used more and more as a substitute for other kinds of flour, largely because of its high protein and fat content and its extremely low carbohydrate content. A strained aqueous suspension of the pulverized beans looks like milk, and is employed as a milk substitute for patients allergic to milk—children as well as adults—and by some bakeries. Soy bean flour is often employed in combination with wheat flour in the preparation of cakes, bread, rolls, pastries, crackers, macaroni, and biscuits, as well as in sauces, coffee substitutes,

certain cereals, cheese preparations, seasonings, ice creams, soups, pork sausage, lunch meats, and other foods. Roasted and salted soy beans are served like nuts. Fresh soy bean sprouts are included in Chinese dishes. Soy flour and lecithin derived from soy beans are used in many commercial candies. Wightman¹⁰⁵⁸ reported asthma due both to ingestion and to inhalation of soy beans.

b) VEGETABLES AND FRUITS

Hypersensitiveness to vegetables is far more common than the literature would seem to indicate. It may well be said that there is no vegetable that has not at one time or other been the demonstrable cause of an allergy. Most commonly encountered, however, and probably also the most severe, are the cases of hypersensitiveness to the legumes (peas, beans, soy beans, lentils, peanuts). Then come, in approximate order of frequency, tomato, carrot, spinach, cabbage, asparagus, rhubarb, celery, onion, and garlic; occasional observations concern sweet potato, white potato, cauliflower, cucumber, turnip, pumpkin, squash, and other vegetables. Zohn⁹⁹¹ has described an unusual case of hypersensitiveness to spinach manifested by gastro-intestinal symptoms and asthma. Of the vegetables found by Hopkins¹⁰⁵⁹ to be the sole nutritional causes of some instances of infantile dermatitis, spinach and white potato were the commonest offenders, being exceeded only by egg, wheat, milk, and orange.

Those vegetables—and the same applies to fruit—that are obtainable only at certain times of the year, can cause seasonal symptoms, while those items that are always available must be taken into consideration all through the year. Cooke⁹⁹ described a pertinent example in a woman with a pruritic eruption about the right eye occurring from June until October of each year and clearly related to the ingestion of tomatoes. Although patch tests were negative, direct local application of fresh juice reproduced the lesions.

Occasional cases have been reported in which the patient is allergic only to the raw and not to the cooked vegetable, and vice versa.

¹⁰⁵⁸ WIGHTMAN, H. B. *J. Allergy* 7: 601, 1934.

¹⁰⁵⁹ HOPKINS, J. G. *Am. J. Dis. Child.* 49: 1511, 1935.

¹⁰⁵⁷ SIMON, F. A. *Letters, Internat. Corr. Club of Allergy*

Skin tests are notoriously misleading in cases of hypersensitiveness to vegetables. The results are very frequently nonspecific, or may show group reactions—for example, positive reactions to all legumes in the presence of a clinical allergy to peas alone. On the other hand, in many cases of allergy skin tests are consistently negative. The reasons for this have been considered elsewhere. Convincingly positive reactions will not infrequently be obtained if fresh vegetable or fruit juices are employed for scratch tests, even though the protein content and sterility are not thereby controlled.

Among the fruits, strawberries, bananas, oranges, grapes, and apples are the principal offenders. There have been occasional reports, however, of hypersensitiveness to pears, cherries, plums, raspberries, gooseberries, and other fruits.

Kahn¹⁰⁹⁰ reported that in southwest Texas, citrus fruits, due to their high rate of consumption, are a leading nutritive allergen, usually causing chronic rhinopathy, urticaria, or dermatitis, and rarely asthma or angioneurotic edema. Skin tests are almost invariably negative. Although berries, apple, peach, apricot, and banana sensitivities are rare in this region, tomato, pineapple, cantaloupe, and watermelon are frequent offenders.

Very interesting was the case of a 22 year old patient observed by the senior author who, after eating tangerines and oranges, regularly complained of headache and showed a bluish violet discoloration of the face due to vascular dilatation, characteristic of the nitritoid crisis. The appearance of these symptoms was effectively prevented by an injection of adrenalin prior to ingestion of the fruit. Other patients after eating oranges have complained of outbreaks of sweating and of a sensation of heat in the head. Hill¹⁰⁹¹ and Goodman and Burr¹⁰⁹² found orange juice to be an important cause of infantile dermatitis, while Hopkins¹⁰⁹³ reported that it is exceeded in this respect only by egg, wheat, and milk. Zahorsky¹⁰⁹⁴ pointed out that orange juice, which contains

about 1 per cent of a readily absorbable protein, is not required by breast fed infants under 4 months of age, or should at least be given with extreme care because of its sensitizing properties. Whether it is the protein, the ethereal oil, or the acid that is the allergen in a given case of hypersensitiveness to citrus fruit, can only be determined by appropriate tests (Urbach and Wiethe¹⁰⁹⁴). When, for example, orange pectin is beneficial the protein of the orange may be assumed to represent the allergenic factor, otherwise, such methods as outlined on page 301 must be employed.

Cooke⁶⁹ described an acute generalized dermatitis following the ingestion of cantaloupe. Although intracutaneous tests were negative, patch tests with the fresh fruit were positive.

Behdjiet observed cutaneous manifestations on an allergic basis produced by ingestion of figs or fig preserves. Kahn¹⁰⁹⁰ reported urticaria due to eating raw figs, along with contact dermatitis from the leaves of the tree.

As a rule, fruit is allergenic only in the raw state—in some cases, however, only when cooked. Occasionally the allergenic action is restricted to certain parts of the fruit (skin, peel, pulp, or seed).

Nuts, particularly peanuts, almonds, Brazil nuts, walnuts, chestnuts, filberts, and pecans, frequently evoke allergies, often severe, usually manifested by rhinopathy, asthma, or urticaria. Peanut butter is included in many home and commercial recipes for candy and cookies. The junior author has observed a severe constitutional reaction, with coma, asthma, generalized urticaria, impalpable pulse, and undetectable blood pressure, within 15 minutes after a known peanut sensitive patient ate one half a cookie that was later determined to have been prepared with peanut butter. Application of a peanut or of a bit of the same cookie to the lower lip for one half minute resulted in marked swelling persisting for several hours.

The following instructions should be given to patients hypersensitive to peanuts (Efron¹⁰⁹⁵):

Peanut may be contacted in
Roasted or salted peanuts

¹⁰⁹⁰ KAHN, S. S. Southern M J 35 8:8 1942

¹⁰⁹¹ HILL, L. W. New England M J 223 624 1940

¹⁰⁹² GOODMAN, HERMAN, and BURR, M. E. Arch. Pediat. 54 88 1937

¹⁰⁹³ ZAHORSKY, J. J. A. M. A. 127 636 1943

¹⁰⁹⁴ URBACH, E. and WIETHE, C. Muenchen med. Wchnschr. 78 2030 1951

¹⁰⁹⁵ EFRON, B. G. Letters Internat. Corr. Club of Allergy Series 7 87 1944

Candy containing peanuts and peanut oil
 Cake made with peanut flour (likely to be used as a substitute for almond flour in macaroons)
 Certain hams from pigs fed peanuts
 Peanut butter, cooking oils, salad oils, salad dressings, shortenings, lard compounds, oleomargarine, canned sardines, packed olives, adulterated olive oil, canned fish, etc
 Cattle feed (peanut oil cake as stock feed)
 Epinephrine in oil—Parke Davis Co Epinephrine in gelatin or sesame oil, the latter prepared by the Winthrop Co., may be substituted

Do not eat peanuts, peanut butter, or foods containing peanuts or peanut flour

Be certain that salad oils, salad dressings, cooking oils, and shortenings do not contain peanut oil Use pure lard, rendered chicken fat Lard fat or Mazola oil

Do not use oleomargarine, canned sardines, packed olives, or canned fish that may contain peanut oil

Do not use milk (or milk products) obtained from cattle which may have been fed peanut oil cake, since the protein is excreted in the cow's milk

Do not eat chocolate candy and candy bars unless you are certain that they are not made with peanut oil

Peanut oil is a high grade oil and is therefore more likely to be found in the more expensive products Many products labeled merely as containing vegetable oils may have peanut oil as an ingredient

Finally, mention should be made here of hypersensitiveness to *chocolate (cocoa)*, which is relatively quite common. Its most frequent clinical manifestations are migraine and allergic rhinitis On the basis of experimental investigations, Joltrain¹⁰⁹ advanced the opinion that the protein components of the cocoa bean are not nearly as active allergenically as is the cocoa butter The question can be decided, in a given case, by administering cocoa propeptan: when this treatment is beneficial, it shows the cocoa protein to be the causal factor; otherwise, it may be the cocoa fat.

c) EDIBLE FUNGI

Among the edible fungi, mushrooms are outstanding as not infrequently allergenic. As an illustration may be mentioned the case of dermatitis following ingestion of certain types of edible mushrooms reported by Hellerstroem.¹⁰⁹⁷ Hypersensitivities to baker's and brewer's yeast and to the molds used in the manufacture of cheese must be included in this category. Yeast is widely employed in

the preparation of raised bread, griddle cakes, fermented beverages such as beer, and some cheeses, it is of course also consumed in the form of yeast cakes. Highly instructive cases have been described by Taub¹⁰⁹⁸ (asthma due to yeast) and by Leopold¹⁰⁹⁹ and Cadrecha Alvarez¹¹⁰⁰ (asthma following the use of taka diastase, which is prepared from *Aspergillus oryzae*) Biederman¹¹⁰¹ was able to trace urticaria and angioneurotic edema to the small quantities of yeast in bread and other baked products. Gutmann's¹¹⁰² case is especially striking: the patient underwent seven laparotomies within six years because of a very severe intestinal spasm simulating an ileus; the true cause of the condition was finally found to be hypersensitiveness to the yeast in beer. In a case observed by the writers, the patient, an elderly man, had for years been suffering from a great variety of allergic symptoms (urticaria, migraine, spasm of the urinary bladder, and renal colic) that disappeared as soon as he desisted from drinking beer Here, as well as in another case, in which the patient suffered from a chronic urticaria, we were able to demonstrate experimentally that the yeast in beer was the causal agent Occasionally there have been patients with hypersensitiveness to the molds used in the preparation of certain kinds of cheese (Camembert, Roquefort, Gammelost).

d) SPICES AND CONDIMENTS

Spices and condiments act as allergens with relative rarity. Mustard, black pepper, and vanilla seem to be the only items worthy of any serious consideration. Avoidance of vanilla is particularly difficult, since it is included in the preparation of so many different foods Isolated cases have been observed, however, in which there was demonstrable hypersensitiveness to *Cayenne pepper (paprika)*, *ginger*, *anise*, *caraway seed*, *saffron*, *nutmeg*, *peppermint*, *cloves*, *poppyseed*, *cinnamon*, and *thyme*. But, in dealing with these substances, one must always bear in mind the possibility of an indirect action due to irritation of the gastro-intestinal mucosa. Owing to this irri-

¹⁰⁹⁸ TAUB, S. J. J. Allergy 3 :285, 1932

¹⁰⁹⁹ LEOPOLD, S. S. Ibid 7, 594, 1936

¹¹⁰⁰ CADRECHA ALVAREZ, J. Información med., vol 6, no 3, 1942

¹¹⁰¹ BIEDERMAN, J. B. J. A. M. A. 106 31, 1936

¹¹⁰² GUTMANN, M. Deutsche med. Wchnschr 59:1281 1933

¹⁰⁹⁶ JOLTRAIN, F. • Les urticaires. Paris, 1939

¹⁰⁹⁷ HELLERSTROEM, S. Acta dermat-venereol 22 331, 1941

tation, undigested or insufficiently digested protein of the ingested food may be absorbed and so come into the blood stream

e) VEGETABLE GUMS

While *gum arabic*, *karaya gum*, and *traga canth* are not foods per se they are often added to prepared foods such as candies, gum drops, ice creams, ice cream powders, gelatin and junket desserts, fillers for commercial pies of the custard variety, some salad dressings, and some diabetic foods. The newer cheese spreads, such as pimento spread and relish spread, may contain as much as 10 per cent of gum stabilizer (tragacanth, karaya, or locust bean). Karaya gum, also known as Indian or Sterculia gum, is contained in emulsified mineral oils and many proprietary laxatives, including Bassaran, Imbicoll, Karaba, and Mucoral. Since it is found in many denture adhesive powders and some tooth pastes, it may be ingested from these sources. The vegetable gums have been observed to elicit urticaria (Bowen¹¹⁰³), gastro intestinal disorders (Figley¹¹⁰⁴), migraine (Alvarez¹¹⁰⁴), and other symptoms. As noted elsewhere they may also act as inhalants and contactants. *Chicle*, the base of chewing gum, was reported to cause allergic rhinopathy (Kleinman¹¹⁰⁵) and laryngeal edema followed by shock like manifestations (Frank¹¹⁰⁶). The possibility of sensitization to *psyllium*, *quince seed*, and other commercial gums should not be overlooked.

f) BEVERAGES

Alcoholic beverages can cause clinical manifestations of allergy, both specifically and non specifically. Their specific action is due to traces of foreign substances that they contain e.g. substances employed in the preparation (or clearing) of the beverage, such as barley, malt and yeast in beer (see p. 312), rye, corn or wheat in whiskey, fish glue egg white isinglass, or yeast in cheap white wine and cheap champagne. In addition, alcoholic beverages are capable of aggravating allergization nonspecifically by increasing the permeability

of the gastro intestinal tract thus facilitating the absorption of insufficiently digested food proteins into the blood stream. It is well known that in many cases of hypersensitivity to oysters for example, the intolerance becomes manifest only when considerable quantities of alcohol are consumed at the same time.

As for the *nonalcoholic beverages* milk and cocoa have been discussed above. Hypersensitivity to coffee is not frequently encountered, and in such cases, according to Gutmann one must differentiate between allergy to coffee, to caffeine, and to surrogates added to the coffee. True coffee allergy is due to the products resulting from the roasting process; therefore, the coffee is tolerated when the greater part of these substances is removed, as in the specially prepared brands of coffee. Reactions are not prevented from appearing, however, by drinking so called caffeine free coffee. The latter is of course recommended in case of hypersensitivity to caffeine. An interesting observation was reported by Funck: a patient suddenly reacted with angioneurotic edema and intestinal spasm to a brand of coffee he had been drinking regularly for years in another locality. Painstaking investigation revealed the fact that the water in the town where he had formerly lived had a high calcium content causing precipitation of the major part of the substances formed during the roasting process, thus rendering them ineffective while the soft water in the locality of his new home merely dissolved these substances. A case reported by De Besche illustrates the necessity of ascertaining and confirming the specificity in every case by means of appropriate experimental controls. An asthmatic child always suffered attacks following ingestion of fish and also after drinking coffee. The response to the latter was found to be attributable to the fishskin commonly used in Norway to clear coffee.

Hypersensitivity to coffee may express itself in a great variety of clinical manifestations. Thus, Gutmann observed itching, neurodermatitis, urticaria, angioneurotic edema, intestinal spasms, diarrhea, gallbladder colic, rhinopathy, and asthma. Adelsberger and Munter¹¹⁰⁹ were able to confirm these find

¹¹⁰³ BOWEN R. Arch. Dermat. & Syph. 39: 506 1939

¹¹⁰⁴ ALVAREZ W. C. J. A. M. A. 114: 1284 1910

¹¹⁰⁵ KLEINMAN A. J. ibid. 104: 455 1935

¹¹⁰⁶ FRANK D. I. Arch. Otolaryng. 32: 1067 1910

ings. Rappaport¹¹⁰⁷ observed severe non-thrombocytopenic hemorrhages from the nose, rectum, and vagina that were due to coffee allergy.

Tea is very rarely the cause of an allergic condition. Bulkley reported the disappearance of a severe resistant dermatitis in a nursing infant after the mother stopped drinking tea. There are isolated reports of hypersensitiveness to camomile tea, sage tea, and others

g) VEGETABLE FATS

Vegetable fats may be allergenically active on account of the minute quantities of protein they contain, but may also act in themselves, possibly through their fatty acids. We have already discussed elsewhere the problem as to whether lipids (as well as carbohydrates) are to be regarded as true allergens or as haptens (see p. 118). In practice, the question can be answered by administering specific propeptans; if they are beneficial, the hypersensitivity is shown to be linked with the protein factor; if not, one may assume the presence of a true hypersensitivity to fat.

Patients sensitive to vegetable oils should be warned about their widespread use, often in mixed form, in a large number of commercially prepared foods, such as sardines, tuna fish, potato chips, doughnuts, popcorn, salted nuts, and cocktail crackers. The possibility of the unannounced substitution of oleomargarine for butter or the adulteration of butter by restaurants, bakeries, and other food handlers, should be kept in mind.

From the allergic standpoint, *cottonseed oil* is by far the most important vegetable fat. It is sold under many trade names, such as Wesson oil, or as salad oil, table oil, or sweet nut oil, as well as under its own generic name. It is widely employed in the manufacture of oleomargarine, Crisco, cottolene, Jewel, Vegtote, and many other shortenings, mayonnaises, and salad dressings. It is frequently used as an adulterant in or substitute for olive oil. Chocolate candies often contain cottonseed oil, and it is used at fruit stands to polish fruit.

Olive oil is frequently adulterated with cottonseed, corn, or other oils. Pure olive

oil, however, has been proved to be the cause of at least a few isolated cases of true hypersensitivity (Vaughan²¹). *Corn oil* is used in salad oils and for shortening in bread and cakes. *Soy bean oil*, which is being increasingly employed, should be kept in mind as a potential food allergen. Like cottonseed oil, which it equals in total quantity of production, soy bean oil is contained in oleomargarine and other butter substitutes, many shortenings, salad dressings, mayonnaises, and baked products. Finally, *nut fats*, such as peanut oil and almond oil, must be mentioned. Instructions for the avoidance of peanut are given above. Hypersensitivity to cocoa butter is discussed on p. 311.

3 CARBOHYDRATES

Hypersensitivity to carbohydrates and intolerance of carbohydrates are, of course, two fundamentally different conditions. The former is a rare allergic phenomenon probably based on a hapten mechanism, while the latter is a metabolic disorder generally considered a forerunner of diabetes. In either case, administration of sugar is followed by the appearance of general or cutaneous manifestations that disappear after elimination of carbohydrates from the diet. In order to differentiate the mechanism, sugar is again given at a time when the patient is free of symptoms, but this is preceded by an adequate injection of insulin. If the manifestations now fail to appear, the case is to be regarded as one of carbohydrate intolerance (latent diabetes), if they reappear, as hypersensitivity to carbohydrates.

We are here concerned only with the latter condition. Both Leiner and Pulay have reported cases of infantile dermatitis in which administration of sugar brought on exacerbation with marked weeping, elimination of sugar resulted in healing. According to Weigert, hypersensitivity to carbohydrates is occasionally the underlying cause of strophulus infantum—a claim the senior writer has twice been able to confirm. Additional reports of allergy to cane sugar have been made by Mathieu, Rowe, Vollbracht, and Schick.

Aside from the 2 cases of strophulus infantum just mentioned, the senior author made the following observation:

¹¹⁰⁷ RAPPAPORT, H. Z. - discussion to Squier and Madison 1964

A man aged 50 presented extensive eczematous changes that were refractory to all therapeutic measures. The glucose tolerance test was perfectly normal nevertheless, in view of the possibility of retention of carbohydrates in the skin alone (Urbach and Lentz¹⁰⁹), a strict diabetic diet was prescribed with the result that the condition soon cleared up. Strangely enough the condition was exacerbated when insulin was administered together with small quantities of carbohydrate. Close observation for several days revealed that the itching and skin manifestations always recurred when carbohydrates were included in the diet. Since insulin did not bring about tolerance of carbohydrates, the presence of genuine hypersensitivity to sugar was assumed. For weeks the patient was kept on a diet that was almost completely free of carbohydrates. These were then cautiously added to the diet in slowly increasing quantities. The patient was soon definitely cured.

In another case, the patient, a woman of 53, had been suffering for several years from recurrent attacks of an intensely pruritic papular eruption. Trial diets (see p 186) disclosed that ingestion of generous portions of carbohydrate foods caused a marked exacerbation of the pruritus and reappearance of the skin lesions, elimination of carbohydrates from the diet was promptly followed by definite improvement.

Hypersensitivity to *honey* should also be mentioned here, a few authenticated cases have been reported. Sometimes the hypersensitivity relates only to certain types of honey, and evidently depends on the source from which the bees have taken the honey. Thus, cases have been reported of urticaria in individuals allergic to buckwheat or to linden, following ingestion of honey from bees that fed on these plants or flowers. It must be remembered, furthermore, that honey frequently contains considerable amounts of pollen, this is capable of eliciting typical symptoms in hay fever patients.

4 SALTS AND ACIDS

Allergic responses to ingested table salt were first reported by Strouse. But it was Gerson who emphasized the importance of table salt as an allergenic factor, particularly in cases of allergic migraine. Vallery Radot and Rouques¹¹⁰ demonstrated the connection between

a severe outbreak of urticaria and hypersensitivity to table salt (based on evidence of positive cutaneous tests with salt, and almost complete disappearance of the urticaria following elimination of table salt from the diet). Gutmann¹¹¹ demonstrated that table salt is a relatively frequent cause of a variety of allergic manifestations (asthma, migraine, urticaria, angioneurotic edema, and neurodermatitis).

Urbach and Willheim¹¹² were the first to undertake a series of investigations along strictly chemical lines, intended to ascertain which of the components of the salt was responsible for the hypersensitivity. Experiments revealed the fact that, in our cases at least, the hypersensitivity was not in relation to salt—sodium chloride—but only to the anion, chloride, the cation, sodium, was tolerated perfectly. These investigations are of importance because they serve to explain why such hypersensitive persons can tolerate salt mixtures that do not contain chlorides—as, for example, curtasal. Furthermore, the same authors succeeded in demonstrating that anions and cations possess mutually antagonistic properties, thus making it possible to neutralize the action of the allergenic anion by increasing the cation content of a salt. A preparation known as titro salt is an example of this kind of salt mixture.

The practical significance of hypersensitivity to salt may be illustrated by an example. FIGURE 131 shows a prurigo like exanthem of about ten years' duration in a woman of 50. The cause of this condition was found to be a hypersensitivity to protein and to spices, which was readily dealt with by means of propeptan treatment and by elimination of pepper and paprika from the diet. Nevertheless, new eruptions and intense pruritus occasionally reappeared. It was observed that these symptoms regularly occurred after ingestion of highly salted dishes. When the patient was put on a salt poor diet, these manifestations promptly receded (FIG 132), they could be made to reappear immediately, however, by administration of 5 Gm of salt in the form of a powder, or by injection of 600 cc of physiologic salt solution. Permanent cure (observation period, three years) was

¹⁰⁹ URBACH E and LENTZ J W. Arch. Dermat. & Syph. 52 301, 1945.

¹¹⁰ VALLÉRY RADOT P and ROUQUES L. Ann. de dermat. et syph. 10 1041 1929.

¹¹¹ GUTMANN M J. Fortschr. d. Therap. 9 427 1933.

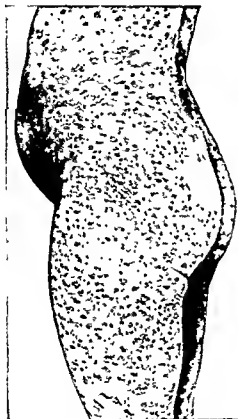
¹¹² URBACH E and WILLHEIM R. Klin. Wchnschr. 11 1012 1932.

achieved by replacing table salt with a chloride-free salt mixture.

Similarly, Urbach and Wilhelm¹³¹ demonstrated the presence of hypersensitivity to certain organic acids and their salts. Here, too, the allergenic action was restricted to the anions. Naturally, experimental testing must be undertaken in every single case, for we have also had occasion to observe patients who were

Such patients can be cured by using distilled water, or by volatilizing the chlorine by boiling the water.

Sour dishes have long been held responsible for the appearance of skin manifestations. Kollert is of the opinion that hypersensitivity to sour apples, which he observed quite frequently, is attributable to the acid. Fuhs reports the case of a woman whose papulo-



LICHEN URTICATUS OF TEN YEARS' DURATION, DUE TO FOOD ALLERGY (EGG, PORK, CARROTS, PEPPER, PAPRIKA, SALT)

FIG 131 Appearance of skin before treatment

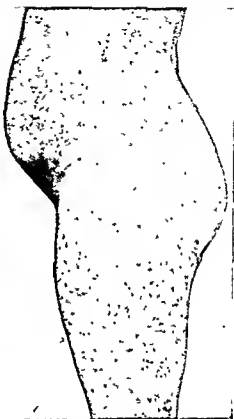


FIG 132 Healing after four weeks of propeptan therapy, use of salt substitute, and elimination of spices

allergic to a number of cations. Elimination of the demonstrably harmful substances brings prompt relief.

Hypersensitivity to the chlorinating chemicals in drinking water has been reported a few times. Watson and Kibler¹³² described a case of asthma and functional colitis from this source, Dutton¹³³ one of dermatitis, and Gutmann¹³⁴ two cases of chronic urticaria.

urticarial exanthem of many years' standing was proved to be provoked by ingestion of sour foods, particularly lemonade. The senior author succeeded in demonstrating that an isolated hypersensitivity to acetic acid (vinegar) was the cause of an urticaria that had recurred for four years, and also of a lichen urticatus (FIG 133) of one year's standing in a girl of 13. The symptoms in the latter case could also be elicited by oral administration of synthetic acetic acid (100 cc of a 3 per cent

¹³² WATSON, S. H., and KIBLER, C. S. *J. Allergy* 5, 197, 1934

¹³³ DUTTON, L. O. *ibid.* 4, 471, 1935

¹³⁴ GUTMANN, M. J. *ibid.* 15, 395, 1944

solution) as well as of 0.5 Gm of acetylsalicylic acid whereas acetic acid neutralized with sodium bicarbonate was tolerated perfectly. If the possibility of hypersensitiveness to acid is kept in mind such cases (caused by vinegar wine oranges lemons pickles etc) will be found much more often than the literature would lead one to suppose.

B DRUGS

Drugs may produce their effects through ingestion injection inhalation contact with or inunction into the skin and very rarely through absorption by the mucous membranes of the mouth, rectum urethra and vagina. In this

31) In allergic hypersensitiveness on the other hand the type of reactive manifestation is entirely independent of the chemical and pharmacodynamic properties of the drug and depends only on which tissue has been allergized. We shall here consider the latter phenomenon i.e. drug allergy exclusively.

Elsewhere we have discussed in some detail the facts indicating that so called drug idiosyncrasy is actually the same as drug allergy. The experimental studies of Obermayer and Pick¹⁵ and particularly of Landsteiner¹⁶ have given strong support to Wolff Eisner's old theory that a non antigenic drug on entering the body may form a compound



FIG. 133. LICHEN URTICATUS DUE TO HYPERSENSITIVENESS TO ACETIC ACID (VINEGAR)

chapter confined to consideration of ingested drugs the discussion will be restricted to those drugs that act by way of the gastrointestinal route. The others will be considered in the appropriate places.

A distinction is made in principle between two types of hypersensitiveness to drugs. The first, frequently called "drug intolerance" consists in an exaggeration of the physiologic action of the drug. For example certain individuals react to 0.01 Gm ($\frac{1}{100}$ grain) of morphine with all the signs of severe morphine poisoning; others react to a single dose of 0.25 Gm ($\frac{1}{4}$ grain) of quinine with buzzing in the ears, nausea and other symptoms. These are manifestations of *toxin hypersensitiveness* attributable to the character of the poison and classified here as nonallergic pathergy (p

antigen with tissue protein or serum protein. Obermayer and Pick¹⁵ iodized proteins thus forming antigens which on injection into animals called forth antibodies specific to itself but not to the original protein. Landsteiner¹⁶ demonstrated that conjugated antigens composed of a drug and a protein can anaphylactize the organism. These studies established the fact that drug allergy can be produced by artificially conjugated proteins. Mulinos and Schlesinger¹⁶ confirmed these findings by experiments on the isolated uterus of sensitized guinea pigs employing the Dale technique. But the question as to the mechanism by which

¹⁵ OBERMAYER F and PICK E. F. *Wien klin Wochensh* 18: 659 1903 17: 26 1904 19: 327 1906

¹⁶ MULINOS M G and SCHLESINGER E. *Proc Soc Exptl Biol & Med* 30: 39 1936

drugs are conjugated in the organism remains unanswered. It cannot be accomplished by simply mixing phenolphthalein, for example, with human serum *in vitro*, but only by enteral or parenteral introduction of this drug into the organism (Rosenthal¹⁵⁹). It would seem that the allergen consists of a compound in which the drug or significant cleavage products of the drug form antigenic combinations with proteins of the host. There are on record a few instances in which the existence of these conjugates has actually been demonstrated. Thus in a case of allergic edema due to acetylsalicylic acid, Oriol¹⁶¹ succeeded in isolating from the patient's urine an aspirin-protease complex which elicited a positive skin test, while both the drug and the protease alone failed to do so. Similarly, Rosenthal¹⁵⁹ recovered a phenolphthalein-serum antigenic complex from the blood of the rabbits in his experiments. The host organism thereafter becomes hypersensitive not only to the simpler drug alone, which represents a "hapten," but to others as well, provided they retain the significant atomic grouping (Zinsser, Enders, and Fothergill¹⁶¹). The nonprotein character of these agents is the basis of the earlier objections to the idea that the same mechanism is operative in drug sensitiveness as in protein allergies; the now well-established theory of the hapten mechanism supplies one of the most important links in the analogy between drug and other allergies.

As regards the clinical occurrence of drug allergy, it is noteworthy that it very frequently appears when medication is resumed after a period of interruption, although it can occur at any time in the course of therapy with either large or small doses. For these reasons there is no reason to consider cumulative effects to be significant. The amounts required to produce allergic manifestations are generally much smaller than those required for pharmacologic or toxic action. Once sensitization has taken place, manifestations are likely to recur after each exposure to the offending or closely related drugs even in small quantity, unless successful therapy is instituted.

It is extremely doubtful whether there is such a thing as a natural drug allergy. The possibility of a hematogenous intra-uterine

sensitization, or of sensitization by way of breast milk or by other antecedent exposure, can almost never be absolutely ruled out.

The diagnosis of drug allergy can be established with certainty only by appropriate avoidance and re-exposure tests. A few other tests have been successfully employed. Duke¹⁶⁰ recommended that, since acetylsalicylic acid (aspirin) is readily soluble in slightly alkaline solutions and therefore in saliva, a small speck of this drug be placed on the tip of the tongue. In allergic individuals, symptoms will appear within one minute; when they do, further absorption can be stopped by repeatedly rinsing the mouth with a teaspoonful of vinegar or dilute acetic acid in a glass of water. A similar technic has been recommended for use before giving diodrast by injection. Blank¹⁶² described a sort of contact test on the buccal mucosa by having the patient hold a tablet of the drug against the mucous membrane for 10 to 20 minutes, the test site being read immediately and in 24 hours. The immediate reaction is edema and occasionally vesiculation around the edge of the area, while the late reaction consists of vesiculation. The junior author has obtained positive results with aspirin, sulfathiazole, sulfadiazine, and codeine. This method appears to be fairly reliable, particularly when positive, and safe. Leftwich¹⁶¹⁷ utilized the serum of patients under sulfonamide therapy with a drug level between 2 and 25 mg per hundred cubic centimeters for tests on cases of suspected sulfonamide hypersensitiveness. It may be postulated that this contains a sulfonamide-plasma protein combination, the drug acting as a hapten. Intracutaneous injection of 0.05 cc. of such serum will in positive cases produce a definite wheal-like response with intense erythema, and the development of pseudopods when the reaction is marked, reaching its maximum in 15 minutes and fading in 30 minutes, while in negative tests and control subjects there is little or no increase in the size of the initial wheal. The criterion for positivity is a difference in size of at least 4 mm. diameter between the test and the control wheals, rather than the absolute size. Rarely, the scratch-patch method (p 177) will produce positive responses when all other

tests are negative, as has been observed by the junior author with penicillin and mercuripurin. In contrast to the usual experience, Pelner¹¹¹⁸ found that his cases with scarlatina form rashes and swelling of the eyes and face due to ingested iodides taken in the form of an iodine-containing saline laxative and in a throat lozenge containing calcium iodide, showed positive reactions to simple patch tests performed by applying a drop of tincture of iodine to the skin.

As a rule, neither intradermal nor patch tests with drugs are capable of eliciting positive reactions, probably because the antigen is not the drug per se, but some derivative formed in the body through oxidation, reduction, or other metabolic processes—the secondary antigen. For the same reason, passive transfer of hypersensitivity fails in cases of fixed drug eruptions, except when Naegeli's transplantation method is used. Dameshek and Colmes¹¹¹⁹ claim that strongly positive reactions can be elicited with a mixture of the drug and the patient's own serum. A positive cutaneous reaction to such "serumized" aminopyrine was also found by Austin¹¹²⁰ to be quite specific for aminopyrine hypersensitivity, and Blank¹¹²⁰ has obtained some promising results with other drugs.

An accurate and comprehensive history is of great help in reaching a diagnosis. The question as to whether drugs have been taken is frequently answered in the negative, for the simple reason that many patients are so thoroughly accustomed to taking their vitamins, laxatives, headache tablets, or aspirin that they no longer regard these preparations as medicine. It is advisable, therefore, to frame such questions not generally, but specifically. Furthermore, it must not be overlooked that certain drugs—or rather, chemicals—are often taken unintentionally and, indeed, without the patient's knowledge. Phenolphthalein may be ingested in many ways other than in the well known laxative preparations. This chemical is often responsible for the pink coloring of mouth washes and tooth pastes and of ice creams and

cake ings. Belote and Whitney¹¹²¹ have catalogued 104 preparations containing phenolphthalein, including intestinal lubricants, stimulants, and antiseptics, and digestants, stomachics, and cholagogues. In the majority of these items, no indication of the presence of the drug is given on the label.

Fresh fruits, vegetables, and also tobacco (Barksdale¹¹²²) often contain appreciable amounts of the arsenic used to combat insects. Wine and cider are likely to contain arsenic for the same reason. As pointed out by Ayres and Anderson,¹¹²³ drinking water in some localities is cleansed with arsenic-containing aluminum sulfate. Of the foods, fish, especially shellfish, naturally contain arsenic, as do milk and eggs when the feed of the animals producing them contains this chemical. Finally, Sulzberger¹ pointed out that in certain districts—e.g., near smelting works—one finds a hundredfold increase in the amount of arsenic in the blood and urine of persons who live on the lee side of blast furnaces.

Bowen¹¹²⁴ has pointed out that ascorbic acid (vitamin C) tablets contain excipients which are capable of causing sensitization.

There are now about 350,000 organic drugs and a few thousand inorganic chemicals used as medicines (Abramowitz¹¹²⁵), and any drug probably can produce an allergic response or other undesirable effects in sensitized individuals. In view of the tremendous number of prescribed dosages and of home remedies, the overall incidence of drug allergy is surprisingly low, and probably less than that due to foods.

Drugs can evoke every type of skin manifestation, and the same drug may elicit the most varied responses in the same patient. Aside from the skin eruptions the following are among the reactions most frequently encountered: asthma, rhinopathy, nausea, malaise, attacks of abdominal cramps and diarrhea, bleeding from the urogenital tract, granulocytopenia, lymphadenopathy, swell-

¹¹¹⁸ PELNER, L. *J. Lab. & Clin. Med.* 27: 1150, 1942.

¹¹¹⁹ DAMESHEK, W. and COLMES, A. *J. Clin. Investigation* 13: 85, 1936.

¹¹²⁰ AUSTIN, V. T. *J. A. M. A.* 120: 911, 1942.

¹¹²¹ BLANK, P. personal communication.

¹¹²² BELOTE, G. H. and WHITNEY, H. A. K. *Arch. Dermat. & Syph.* 36: 2-9, 1937.

¹¹²³ BARKSDALE, E. E. *J. A. M. A.* 115: 672, 1940.

¹¹²⁴ AYRES, S. JR. and ANDERSON, N. P. *ibid.* 97: 437, 1931.

¹¹²⁵ BOWEN, R. *Letters Internat. Corr. Club of Allergy Series* 5: 68, 1941.

¹¹²⁶ ABRAMOWITZ, E. W. M. *Clin. North America* 22: 1323, 1938.

ing of the joints, pain in the extremities, fever, nitritoid crisis, and finally, anaphylactic death.

Among the skin manifestations, the following are more or less commonly observed: acute (FIG. 134) and chronic (FIG. 135) dermatitides; polymorphous erythemas (FIG. 136),

like dermatoses, exfoliative dermatoses; purpura; acneform (FIG. 141), nodular, ulcerative, pemphigoid, and vegetative drug eruptions (FIG. 142). The skin manifestations are usually generalized, but may be restricted to certain areas—the face, for example, or the

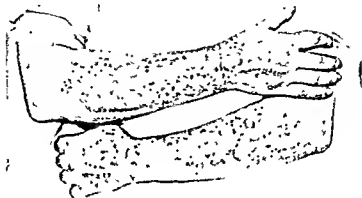


FIG. 134 DERMATITIS DUE TO ORAL ADMINISTRATION OF DIGITALIS

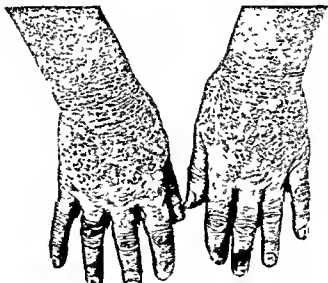


FIG. 135. CHRONIC DERMATITIS OF HANDS AFTER PROLONGED INGESTION OF SODIUM SALICYLATE USED AS PRESERVATIVE IN CANNED FRUIT

morbilliform (FIG. 137), scarlatiniform (FIG. 138), and pityriasis-rosea-like types, less frequently, bullous (FIG. 139) or erysipeloid exanthems; occasional enanthems (stomatitis), fixed drug eruptions (FIG. 140); urticaria; angioneurotic edema; erythema exudativum multiforme; erythema nodosum; lichen-ruber-

leg. Even palmar dermatoses may be caused by commonly used drugs, such as the sulfonamides, especially sulfapyridine, iodine and bromine containing compounds, antipyrine, arsenic and gold compounds, and insulin (Anderson¹²⁸). Skin lesions due to drugs are

¹²⁸ ANDERSON, H. H. Correspondence, J. A. M. A. 129, 766, 1943.



FIG 136 POLYMORPHOUS ERYTHEMA DUE TO BARBITAL

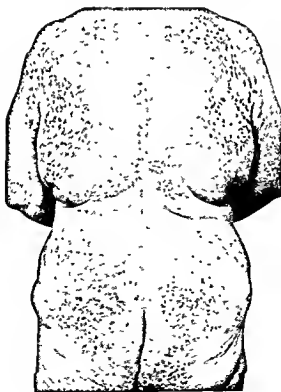


FIG 137. DISSEMINATED DERMATITIS FOLLOWING USE OF PHENOBARBITAL

often arranged in a symmetric pattern. As a general rule, they are of sudden onset, pinkish to purplish in color, asymptomatic, and afebrile. They are likely to appear within the first two weeks of treatment, or, as so often noted, when the drug is again administered after a rest period.

The clinical picture of allergic drug exanthems is only rarely characteristic for a certain chemical, such as bromides (Fig. 142),

on the body is "fixed"—i.e., that a previously affected area can be activated by re-exposure



FIG 138 GENERALIZED QUININE DERMATITIS

iodides (Fig. 141), phenolphthalein (Figs 140, 145, 146), and antipyrine (Figs. 144, 147)

Table 32 summarizes the most common allergic symptoms along with the drugs that are most likely to produce them. Table 33 reviews the more important drugs in alphabetical order, together with the allergic symptoms that each most frequently evokes.

The fixed drug eruptions merit special consideration here. The term "fixed" does not refer to the duration or persistence of the lesion, nor to the residual pigmentation, but solely to the fact that the location of the lesion

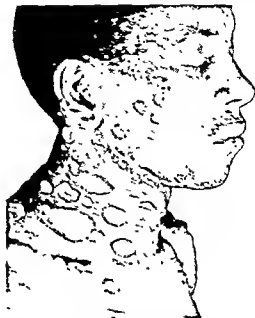


FIG 139 HYPERSENSITIVENESS TO SULFATHIAZOLE RESULTING IN GENERALIZED BULLOUS ERUPTION

Case of 25 year-old Negro locally treated with sulfathiazole ointment for diffuse pyogenic infection on legs. Same therapy was employed for three relapses in period of one year. For fourth relapse he was given sulfanilamide by mouth and developed erythema within six hours. Six months later, because of intractableness of pyogenic skin disease, chemotherapy was again attempted with 0.5 Gm. of sulfathiazole, and was followed in two hours by generalized bullous eruption. (Courtesy Drs. D. M. Pillsbury and C. S. Livingood)



FIG 140 FIXED DRUG ERUPTION DUE TO PHENOLPHTHALEIN HYPERSENSITIVENESS

to the drug or other excitant. The typical lesion is a round or oval plaque, often edematous, and rather sharply defined. Its size



FIG 141 HYPERSENSITIVENESS TO IODIDE ADMINISTERED FOR ASTHMA (IODODERMA)



FIG 142 BROMIDE HYPERSENSITIVENESS IN EPILEPTIC PATIENT (BROMODERMA)

varies from that of a small coin to that of the palm of the hand (FIG 143). The number of lesions in a given case may range from one (FIG 143) to as many as several dozen (FIG 144). The color is usually wine red at first later becoming violaceous and finally slate bluish. The affected site frequently shows a residual pigmentation of varying degree and duration (FIG 146). Vesicles are occasionally formed with subsequent desquamation or crust formation. Fixed eruptions are not infrequently located in the mucosa of the mouth and genitalia (FIG 147); they are likely to be vesicular or pemphigoid in character.

For many years the opinion was generally held that fixed drug eruptions were almost always due to antipyrine, acetphenetidin and phenolphthalein. This view was finally and effectively exploded however by Abramowitz and Noun¹¹²⁷ and by Chargin and Leifer¹²⁸ when they published their admirable compilations of all the pertinent cases in the literature along with the cases they themselves had observed (due to sulfonamides, salicylates, barbiturates, etc.). Furthermore Abramowitz and Russo¹¹²⁹ have recently made a compilation of agents other than drugs that can produce the same clinical picture even including foods as for example lentils (Urbach¹³⁰) and tomatoes (Cooke¹³⁰⁷).

The fact that fixed drug eruptions are of allergic nature has been proved by means of the passive transfer of the hypersensitivity (autotransplantation method) by Naegeli,⁶⁶⁹ Knowles,⁶⁷⁰ and Urbach.⁶⁷¹

The senior author¹³⁰ as well as Loveman¹³¹ has shown that although epidermal and cutaneous tests with the drugs constantly fail to elicit reactions in normal skin sites they are positive when performed on previously affected areas. This coincides with the known fact that transfer of the hypersensitivity can be achieved only with pigmented—i.e. with specifically allergized—epidermis.

Space does not permit even a brief resume of the huge number of reports of sensitivity to

¹¹²⁷ ABRAMOWITZ, E. W. and NOUN, M. H. *Arch. Dermat. & Syph.* 35: 875, 1937.

¹¹²⁸ CHARGIN, L. and LEIFER, W. J. *Invest. Dermat.* 3: 443, 1940.

¹¹²⁹ ABRAMOWITZ, E. W. and RUSSO, J. J. *Arch. Dermat. & Syph.* 41: 707, 1940.

¹³⁰ URBACH, E. *Zentralbl. f. Bakt. u. Suppl. h. 39*: 37, 1932.

¹³⁰⁷ LOVEMAN, A. B. *J. A. M. A.* 102: 97, 1934.

various drugs, so that only those of unusual nature or importance may be considered Of *Codeme*, *morphine*, *strychnine*, *emetine*, *ephedrine*, *quinine*—practically every known

TABLE 32—*Clinical Symptoms Due to Drugs*

Type of Symptoms	Drugs
Erythematous eruptions morbilliform and scarlatiniform erythemas, exfoliative dermatitis	acetylsalicylic acid, aminopyrine, antipyrine, arsenicals, balsams, barbiturates, belladonna, bismuth, chloral, cinchophen, codeine, digitalis, emetine, ephedrine, iodides, mercury, methenamine, morphine, opium, phenobarbital, phenolphthalein, quinine, salicylates, sulfonamides
Eczenatous eruptions	arsenicals, chloral, ephedrine, mercury, procaine, quinine
Urticaria, angioneurotic edema	acetphenetidin, acetylsalicylic acid, aminopyrine, antipyrine, arsenicals, atropine, belladonna, bromides, cinchophen, digitalis, dinitrophenol, ephedrine, emetine, iodides, morphine, opium, phenobarbital, phenolphthalein, quinine, salicylates, sulfonamides
Erythema-multiforme-like eruptions	acetphenetidin, aminopyrine, antipyrine, iodides, phenolphthalein, salicylates, sulfonamides
Bullous eruptions	antipyrine, bromides, chloral, iodides, quinine, phenobarbital, phenolphthalein, salicylates
Acneform eruptions	bromides, chloral, iodides
Pemphigoid, vegetative, ulcerative eruptions	bromides, iodides, sulfonamides
Fixed eruptions	acetphenetidin, aminopyrine, antimony, antipyrine, arsenicals, barbiturates, bismuth, cinchophen, emetine gold, mercury, phenolphthalein, quinine, salicylates, sulfonamides
Pruritus	acetylsalicylic acid, aminopyrine, antipyrine, belladonna, codeine, ipecac, mercury, morphine, opium, phenobarbital, sulfonamides
Granulocytopenia	aminopyrine, dinitrophenol, sulfonamides
Fever	antipyretics, iodine, mercury, quinine, sulfonamides
Asthma	acetylsalicylic acid, hyoscyamus, ipecac, quinine, sulfonamides
Rhinopathy	acetylsalicylic acid, antipyrine, iodides, quinine
Purpura	arsenicals, aspirin, balsams, barbiturates, colchicine, dinitrophenol, ephedrine, ergot, gold, iodides, mercury, nirvanol, opium, quinine, salicylates, sedormid, sulfonamides, thiouracil
Photosensitization	sulfonamides, barbiturates

those ingested, the sulfonamides, barbiturates, alkaloids, and analgesics probably are of prime significance.

alkaloid—have been reported as capable of sensitizing and of producing eczematous contact-type dermatitis. This dermatitis may

TABLE 33—Symptoms of Drug Allergy

Drug	Symptoms
Acetanilid	erythematous erupt on
Acetphenet d n	erythematous urticarial or circumscribed fixed types of eruptions erythema multiforme
Acetylsalicylic acid (Aspirin)	asthma rhinopathy urticaria angioneurotic edema Pruritus scarlatiniform erythema purpura anginoid symptoms abdominal cramps shock collapse death
Allonal	see Barbiturates
Aminopyrine	scarlatiniform exanthem erythema multiforme like eruption urticaria pruritus agranulocytosis
Antipyrine	morbiliform or scarlatiniform erythema fixed erythematous or bullous localized pigmented eruptions sometimes involving mucous membranes purpura urticaria
Arsenic	erythematous morbilliform scarlatiniform eczematous papular bullous or pustular eruptions generalized exfoliative dermatitis angioneurotic edema asthma
Atropine	see Belladonna
Barbiturates	morbiliform eruptions urticaria localized fixed pigmented eruptions photosensitization
Belladonna	erythematous patches with pruritus scarlatiniform eruptions asthma
Bismuth	erythematous eruptions bullous or hemorrhagic lesions
Bromides	acneiform furunculoid pustular nodose tuberculous bullous ulcerative or vegetative eruptions
Chloral	maculovesicular or scarlatiniform erythemas eczematous eruptions acneiform lesions
Cinchophen	urticarial or erythematous eruptions angioneurotic edema
Codine	see Opium
Digitalis	erythematous scarlatiniform or papular eruptions urticaria angioneurotic edema
Dinitrophenol	urticaria granulocytopenia
Ephedrine	erythematous or eczematous eruptions urticaria purpura
Emetine	morbiliform or urticarial eruptions
Ergot	purpura
Iodides	acneiform pustular papular nodular bullous urticarial purpuric or vegetative eruptions angioneurotic edema rhinopathy
Ipecac	pruritus erythema asthma

TABLE 33—*Concluded*

Drug	Symptoms
Mercury	pruritus, erythematous, eczematous, scarlatiniform eruptions, generalized exfoliative dermatitis, purpura
Methenamine	localized erythematous lesions, generalized morbilliform eruptions
Morphine	see Opium
Opium	erythematous, morbilliform, scarlatiniform, or urticarial eruptions that itch intensely and are usually followed by desquamation
Phenacetin	see Acetphenetidin
Phenobarbital	generalized pruritus, erythematous or bullous eruptions, including mouth and genitals, urticaria, localized fixed pigmented eruptions
Phenolphthalein	erythematous or bullous eruptions, erosive lesions in mouth and on genitals; fixed erythematous or bullous pigmented lesions
Quinine	erythematous, eczematous scarlatiniform eruptions, followed by desquamation, fixed pigmented erythema, urticaria, angioneurotic edema, thrombocytopenic purpura, rhinopathy, asthma, gastro intestinal symptoms, fever
Salicylates	erythematous or scarlatiniform eruptions followed by desquamation, purpura
Sulfonamides	erythematous papular, bullous, morbilliform, scarlatiniform erythemas, exfoliative dermatitis, photosensitivity, pruritus, urticaria, angioneurotic edema, purpura, fixed drug eruptions, lymphadenopathy, hepatitis, granulocytopenia, leucemoid reactions, hemolytic anemia, perianteritis nodosa, diarrhea; fever, asthma, nephritis
Thiouracil	leucopenia, granulocytopenia, fever, erythematous maculo papular dermatitis, purpura, generalized lymphadenopathy, swelling of submaxillary salivary glands, jaundice, arthralgia

be elicited by both external exposure and hematogenous distribution to the skin after absorption. Many of these alkaloids also cause urticarial reactions and other manifestations, such as asthma or rhinopathy. The cutaneous eruptions due to codeine have been described by Seidmann.¹¹² Ephedrine may be absorbed when used in the form of nose drops, as in 10 cases of dermatitis observed by Abramowitz,¹¹³ and in 1 case with a bullous eruption on the hands and feet from the same source reported by Lewis¹¹⁴; in this patient a strongly positive vesicular patch test and an urticarial intracutaneous test were obtained with a 1:1000 dilution of

ephedrine hydrochloride. Engelscher¹¹⁵ reported an extensive and prolonged dermatitis with ridging of the nails in a 14-year-old asthmatic, appearing eight hours after a single dose of 16 mg ($\frac{1}{4}$ grain) of ephedrine sulfate. Desquamation of the affected areas persisted for many weeks. Although quinine sensitivity is rare, Urbach¹¹⁶ reported an eruption due to this drug (Fig. 138), and Braun, Czertok, and Kornbleuth¹¹⁷ a patient with hyperpyrexia, diarrhea, abdominal pain, rigor, and vomiting, in whom patch tests were positive. In 2 cases observed by Rose¹¹⁸ with eruptions on the trunk and proximal portions of the

¹¹² SEIDMANN, M.: Arch. Dermat. & Syph. 47: 654, 1943.

¹¹³ ABRAMOWITZ, E. W.: Brit. J. Dermat. 45: 225, 1933.

¹¹⁴ LEWIS, G. M.: Arch. Dermat. & Syph. 49: 379, 1944.

¹¹⁵ ENGELSCHER, D. L.: New York State J. Med. 43: 307, 1943.

¹¹⁶ BRAUN, K., CZERTOK, J., and KORNBLEUTH, W.: Tr. Roy. Soc. Trop. Med. & Hyg. 37: 221, 1943.

¹¹⁷ ROSE, W. M.: J. A. M. A. 123: 955, 1943.

extremities swelling of the penis and scrotum and painful micturition the only contact with



FIG 143 FIXED DRUG ERUPTION DUE TO AMIDOPYRINE HYPERSENSITIVENESS



FIG 144 DISSEMINATED ANTIPYRINE EXANTHEM

the drug previous to its ingestion as a malaria repressive measure was with the quinine containing contraceptives employed by the pa-

tients wives Both fixed and generalized eruption in the same patient unusual when occurring at the same time—from quinidine was described by Colschlag¹³

Of the *barbiturates* Moss and Long¹⁴ found that about 5 per cent of patients react unfavorably to phenobarbital of which those with whealing and pruritus are due to sensitization while those with morbilliform or scarlatiniform maculopapular eruptions (FIG 135) often with fever conjunctivitis stomatitis and pharyngitis are thought to be toxic The two types do not usually occur in the same patient Other barbiturates have similar effects (FIG 136) Potter and Whitacre^{14a} reported an unusual case of chills fever diffuse eruption with desquamation and progressive anemia due to sensitivity to phenobarbital and amytal Diphenylhydantoin sodium (phenytoin sodium dilantin sodium) is known to produce a wide variety of dermatoses in a fairly large percentage of cases and has been responsible for at least one case of a fixed type of drug eruption (Barton and O'Leary^{14a}) Other cutaneous reactions caused by this drug include morbilliform and scarlatiniform erythema exfoliative dermatitis urticaria bullous ecchymotic purpuric and petechial eruptions and even a fatal hemorrhagic erythema multiforme

Acetylsalicylic acid (aspirin) and related antipyretics and analgesics may be responsible for a wide variety of allergic manifestations among which may be mentioned fever asthma (van Leeuwen¹⁴) laryngeal edema (Muench^{14b} Borries^{14c}) bullous dermatitis (FIG 11) and fixed drug eruptions (FIGS 143 144 147) Hurst^{14d} described gastric hemorrhage following the ingestion of aspirin tablets and presumably on an irritative and not an allergic basis but Honigsberger^{14e} reported that the hemorrhagic effects were not

¹³ COLSCHLAG G. M. J. Aug 1932 2 501 1942

¹⁴ MOSS R. E. and LONG W. E. A. J. Derm. & Syph. 46 386 1942

^{14a} POTTER J. K. and WHITACRE R. J. Ann. Int. Med. 21 1041 1944

BARTON R. L. and O'LEARY P. A. A. J. Derm. & Syph. 48 413 1943

LEEUEWEN W. S. and Muenchen med. W. hnschr. 5 1588 1928

^{14b} MUECHEN Zts. f. Hals Nasen u. Ohrenh. 20 274 1928

^{14c} BORRIES G. V. T. Otolaryng. (Fukuoka) 3 671 1930

HURST A. B. J. M. J. 1 768 1943

^{14e} HONIGSBERGER M. B. M. J. 2 57 1943

limited to the stomach and described 3 cases of epistaxis following the absorption of this drug, although definite proof of allergy is lacking. Fatal cases of thrombocytopenic purpura due to sodium salicylate were reported by Ashworth and McKemie¹⁵⁷ and Rappaport et al.¹⁵⁸

erally conceded that such untoward effects are probably on an allergic basis, analogous to the undesirable manifestations produced by the sulfonamides (Gargill and Lesses¹¹⁴⁵), since the clinical phenomena show much parallelism, although the drugs are structurally unrelated. The commonest effect is fever or



FIG 145 Appearance of fixed drug eruptions twenty four hours after ingestion of drug



FIG 146 Persistence of slate gray pigmentation three months later

PHENOLPTHALEIN HYPERSENSITIVENESS

The new drug *thiouracil* has been found to cause "toxic" reactions in 10 to 20 per cent of cases of hyperthyroidism treated, although Cookson¹¹⁶⁶ estimated the total incidence as 23 per cent, and Gabrilove and Kert¹¹⁴⁷ noted complications in 3 of 9 patients, this proportion being approximately maintained in a larger series (Gabrilove et al.^{1167a}). It is gen-

leucopenia, and the most serious granulocytopenia, which may terminate fatally (Ferrer, Spam, and Cathcart,¹¹⁶⁸ Gargill and Lesses,¹¹⁴⁵ Lahey et al.¹¹⁶⁹ and others). In the experience of McArthur, Rawson, and Means^{1170a} fever was the most conspicuous fea-

¹¹⁶⁶ COOKSON, H. *Lancet* 2: 485, 1945

¹¹⁶⁷ GABRILOVE, J. L., and KERT, M. *J. J. A. M.* 4: 124, 504, 1944

^{1167a} GABRILOVE, J. L., KERT, M. J., and SORTER, L. *J. Am. Int. Med.* 23: 537, 1945

¹¹⁶⁸ GARGILL, S. L., and LESSES, M. F. *J. A. M. A.* 127: 890, 1945

¹¹⁶⁹ FERRER, M. I., SPAIN, D. M., and CATHCART, R. T. *ibid.* 127: 646, 1945

¹¹⁷⁰ LAHEY, F. H., BARTELS, F. C., WARREN, S., and MEISSNER, W. A. *Surg., Gyn. & Obst.* 81: 429, 1945

^{1170a} MCARTHUR, J. W., RAWSON, R. W., and MEANS, J. H. *Ann. Int. Med.* 23: 919, 1945

ture of the reaction in approximately 5 per cent. Other prominent manifestations include urticarial erythematous maculopapular morbilliform and dermatitic eruptions generalized lymphadenopathy swelling of the salivary glands jaundice purpura anemia diarrhea arthralgia arthritis and edema particularly of the extremities. Cooperative studies^{139b, 140c} involving several thousand patients indicate the incidence of these complications to be approximately as follows: death 0.4 to 0.5 per cent, fever 3 to 5 per cent, leucopenia 3 to 4.4 per cent, agranulocytosis 1.8 to 2.5 per cent, skin reactions 3.3 per cent.



FIG 147 FIXED DRUG ERUPTION DUE TO ANTIFVRINE HYPERSENSITIVENESS

Location and appearance of lesion which as confined to glans penis could readily cause erroneous clinical diagnosis of syphilis

glandular enlargement about 5 per cent and other manifestations about 2 per cent. Patients with edema of the legs rash nausea vomiting diarrhea and enlarged salivary glands can sometimes continue the medication with reduced dosage (Williams and Clute¹⁴¹). Untoward reactions usually appear within the first four to eight weeks of treatment or after repeated courses. In 2 cases McGavack et al.^{141a} were able to reproduce the

syndrome of chills high fever urticaria and grippe like symptoms within six hours by a single dose of the drug. Their attempts at hyposensitization were unsuccessful.

Finch¹⁴² holds that the unpleasant side effects following administration of *diethylstilbestrol* particularly nausea and vomiting but also including abdominal pains and migraine are an allergic response occurring only in women who had previously had nausea and vomiting of pregnancy and who had presumably been sensitized to the secretions of their own gravid corpus luteum at that time. All such cases had negative skin tests to diethylstilbestrol but positive to luteal hormone. The allergen must be some substance produced secondary to stimulation from diethylstilbestrol or a metabolic by product or end product of its metabolism probably the former. Hyposensitization with small and gradually increasing doses was invariably successful. Severe angioneurotic edema of various portions of the body was observed by Saphir and Weinglass¹⁴³ strongly positive intracutaneous reactions were obtained and the symptoms disappeared when the drug was discontinued.

The widespread and ever increasing use of the *sulfonamides* and the host of patients who have been sensitized to them justifies consideration of this topic at length. Long¹⁴⁴ estimated that possibly 10 to 15 million people received one of the sulfonamide derivatives in one year in this country and review of large series of cases indicated a total of 11.9 per cent complications with sulfanilamide 13.9 per cent with sulfapyridine 18.9 per cent with sulfathiazole and 6.5 per cent with sulfadiazine. There has been insufficient experience with sulfamerazine to arrive at an adequate evaluation of its sensitizing properties but it probably compares with sulfadiazine in this respect. Sulfaguanidine and succinylsulfathiazole (sulfasuxidine) give rise to untoward effects far less commonly than the others probably due to their poor absorption from the intestinal tract. However the junior author has seen an acute severe generalized vesicular

^{139b} MOORE F D J A M A 130 315 1946

^{140c} WICKLE W V JR HARDY S M HAZEL G R HINES D C NEWCOMER H S SHARP E A and SISK W N b d 130 343 1946

WILLIAMS R H and CLUTE H M b d 128 6 1945

¹⁴¹ MCGAVACK T H MORTON J H VOGEL M and SCHWIMMER D J Clin Endocr vol 5 259 1945

¹⁴² FINCH J W J A M A 119 400 1942

¹⁴³ SAPHIR W and WEINGLASS A R b d 119 57 1942

¹⁴⁴ LONG P H discussion on Sulf W D e al b d 121 307 1943

dermatitis persisting for 10 days, following a single test dose of 0.25 Gm. of sulfaguanidine in a patient who had been sensitized months previously during treatment for bacillary dysentery.

Brown¹¹⁴ has reviewed the subject of allergy to the sulfonamides.

Sensitivity to the sulfonamides most frequently appears between the eighth and fourteenth days of treatment and appears to depend more on the factor of time than on the total dose employed (Erskine¹¹⁵). Kent and Diefendorf,¹¹⁷ however, found that neither factor was significant. Delayed reactions may appear up to 48 hours after chemotherapy has been stopped, so that administration for more than 6 days makes sensitivity a possibility. It is particularly likely to occur during a second or third course of therapy at various intervals of time, occasionally quite long. Under such circumstances, reaction to the first and small doses is not unusual. Despite an overwhelming number of reports confirming this influence of repeated courses, Green, Steckel, and Michener¹¹⁸ found that the nature, incidence, and severity of untoward reactions to the readministration of sulfathiazole in both patients and control subjects were not significantly different from those of the first course. This was true up to five courses of treatment. Moreover, they observed reactions as early as the second day following the initial dose, before there had been time for sensitivity to develop. Unlike most observers, they felt that the level of dosage was a factor in determining the tolerance. Hence, without minimizing the possible toxicity of these drugs, the nature of which is not clear, they believe that it is not a hypersensitivity, and that the danger of repeated doses has been overemphasized.

Almost all authorities, however, are in agreement both on the possibility of sensitization to sulfonamides, capable of verification by various clinical and test methods, and on its potential dangers. Hence, it must be strongly emphasized that these drugs are not to be used

haphazardly and without clear clinical indications. Their careless employment in minor or self-limited diseases is to be soundly condemned—lest the cure be worse than the disease. There is reason to think that an increasingly large portion of our population is being sensitized, and that such allergization will persist for long periods of time, rendering necessary and even life-saving chemotherapy impossible when it is really needed. The sulfonamides should be reserved for infections in which they have been proved efficacious and which are severe, potentially dangerous, or extending. Patients should always be carefully questioned about previous sulfonamide therapy, both systemic and local, and especially about possible untoward manifestations. If the disease is such as to allow delay in treatment and any uncertainty exists, a single test dose of 0.5 Gm. may be tried and the patient observed for several hours for allergic effects.

It is also important to know that patients are often sensitized by local application of sulfonamides to diseased skin in the form of ointments or powders, thereby leading to untoward reactions on subsequent internal administration. Livingston and Pillsbury¹¹⁹ described 12 such cases, all characterized by malaise, fever, exacerbations of local symptoms, and a generalized hematogenous "id"-like eruption which was "explosive" in its onset (Fig. 139). They properly warn that the indications for the use of topical sulfonamide therapy should be carefully weighed, and that it should not be continued for more than 5 days. Shaffer, Lentz, and McGuire¹²⁰ performed Prausnitz-Kuestner and Urbach-Koenigstein passive transfer tests with the serum and blister fluids of 4 such cases. Strong immediate urticarial and delayed tuberculin-type reactions were obtained with the former method and highly suggestive responses with the latter, indicating the presence of both circulating and tissue antibodies. It is to be noted that the original local sensitizing exposure to the sulfathiazole may or may not have resulted in local dermatitis at the time.

¹¹⁴ BROWN, E. A. *Ann Allergy* 1: 164, 1943

¹¹⁵ ERSKINE, D. *Lancet* 2: 568, 1942

¹¹⁷ KENT, G. T., and DIEFENDORF, H. W. *Am J M Sc* 209: 640, 1945

¹¹⁸ GREEN, R. C., STECKEL, M. L., and MICHENER, J. M. *Mil Surgeon* 83, 369, 1943

¹¹⁹ LIVINGSTON, C. S., and PILLSBURY, D. M. *J A M A*, 121: 406, 1943

¹²⁰ SHAFFER, B., LENTZ, J. W., and MCGUIRE, J. A.: *ibid.*, 123: 17, 1943

The eruption precipitated by ingestion of the drug tends to begin and be most severe at sites where the sulfathiazole was applied locally, although it may later disseminate widely, and it may mimic the eruption under treatment. Pyogenic sensitivity, especially to the *Staphylococcus*, appears to be a predisposing factor to the sensitization particularly chronic impetiginous dermatitis, rather than impetigo, ecthyma, or acute pyogenic complications of fungous infections or of acute contact dermatitis. The cases described by Ellis¹⁶¹ differed in giving positive direct patch tests to sulfathiazole. There is evidence that vehicles containing lanolin or cholesterol compounds increase the possibility of sensitization to the drug. Numerous other authors, including Cohen, Thomas, and Kalisch¹⁶² and Burgess¹⁶³ have reiterated the necessity of considering this source of allergization and of caution in administering sulfonamides by mouth if local therapy has been used previously. Fisher¹⁶⁴ found that in 100 patients in whom local or general dermatitis followed the local application of sulfanilamide, the skin rash could be again evoked by a single oral dose of 0.5 Gm of the drug. The incorporation of sulfonamides in commercial ready prepared bandages for minor wounds is unsound for the reasons given above. There is every reason to believe that sulfonamide containing gargles, chewing gums, nose drops, nose and throat sprays, intranasal and intra-tracheal instillations may act in the same way. The routine use of suspensions of sulfonamides for the prevention of impetigo in nurseries is also potentially dangerous.

Evidence that even small doses of these drugs may produce reactions is found in the experience of Lee¹⁶⁵ that a single dose of 2.0 Gm of sulfadiazine elicited untoward effects in 128 cases among 25,000 subjects. Although most of these were mild, in 3 patients hyperpyrexia and mental disturbances ensued, while in 6 the symptoms persisted for 3 days and even as long as two weeks.

Black Schaffer,¹⁶⁶ in necropsies of 5 cases of fatal reactions following therapeutic use of sulfonamide compounds found the basic lesion, as in experimental protein anaphylaxis, to be a necrotizing fibrinoid arteritis of the smaller vessels. The cellular exudate was monocytic in composition. The reticuloendothelial system was hyperplastic and the sinusoids were crowded with macrophages showing phagocytosis of erythrocytes and leucocytes. This phenomenon was thought to be the morphologic expression of the addition of some substance to the blood cells (possibly a conjugated sulfonamide group) rendering them foreign. Black Schaffer suggested the possibility that these homologous "foreign cells" may elicit the production of antibodies—an instance of endogenous allergy—and may account for the hemolytic anemia, the leucopenia and the agranulocytosis.

Ingestion of sulfonamides may give rise to a great many allergic manifestations, including a wide variety of skin eruptions, photosensitivity, conjunctivitis, granulocytopenia or agranulocytosis, hemolytic anemia, thrombocytopenic purpura, generalized lymphadenopathy, hepatosplenomegaly, fever, polyneuritis, asthma, hepatitis, nephritis or nephrosis, and periarthritis nodosa. Several of these conditions in any one patient are the rule. Certain renal complications of hematuria, oliguria, azotemia, and urinary concretions are thought to be not on an allergic basis but rather the result of purely mechanical effects due to the precipitation of sulfonamides and their acetylated forms in the renal tubules and pelves, or in the ureter and bladder. Such disturbances as nausea, vomiting, headache, vertigo, transient mental effects (confusion, delirium, excitement, depression, even psychoses), and peripheral neuritis are attributed to toxic effects of the sulfonamides, especially sulfanilamide and sulfapyridine, on the central and peripheral nervous system. Cyanosis, due to the formation of methemoglobin and rarely of sulfhemoglobin, and acidosis, both often caused by sulfanilamide, are also pharmacologic effects. None of these non-allergic conditions will be discussed here.

The skin rashes due to sulfonamides are commonly of the erythematous, morbilliform,

¹⁶¹ ELLIS F A Southern M J 37 493 1941

¹⁶² COHEN M H THOMAS H B and KALISCH A C J A M A 121 408 1943

¹⁶³ BURGESS J F Canad M A J 51 25 1944

¹⁶⁴ FISHER B M J Australia 31 449 1944

¹⁶⁵ LEE R V J A M A 126 630 1944

¹⁶⁶ BLACK SCHAFFER B Arch Path 39 301 1945

scarlatiniform, bullous, urticarial, or purpuric types, although erythema-nodosum-like lesions also occur. Splenomegaly and generalized lymphadenopathy or fever may be associated with skin eruptions. Desquamation may follow the scarlatiniform type. In rare instances, ulcerations of the buccal or gingival mucosa may occur. The appearance of a mild erythematous eruption is not always an indication for immediate discontinuance of sulfonamide therapy. Among the less common forms the following may be mentioned, generalized exfoliative dermatitis due to sulfadiazine (Johnson¹¹⁶⁷), fixed drug eruption from sulfadiazine and sulfamerazine (Freeman¹¹⁶⁸), and associated with conjunctivitis and fever from sulfathiazole (Director¹¹⁶⁹); fatal bullous dermatitis from sulfamerazine (Greenberg and Messer¹¹⁷⁰), and from sulfadiazine (Dardinski¹¹⁷¹); and nearly fatal generalized pemphigus-like reactions with fever due to sulfadiazine (Raffiello and Nichols¹¹⁷²) and to sulfamerazine (Kasselberg¹¹⁷³). Erythema multiforme-like eruptions and purpura have also been observed. Photosensitization not infrequently occurs in patients receiving sulfonamides for more than 6 days and will be manifested by a dermatitis of exposed parts. The active wave-length was found by Blum¹¹⁷⁴ to be shorter than 3200 Angstrom units. In the military experience of Park and Platts¹¹⁷⁵ in the Middle East, 4.3 per cent of a group receiving sulfanilamide and 1.9 per cent of those receiving sulfapyridine developed light dermatitis of the parts of the body currently or previously exposed to light. Peterkin¹¹⁷⁶ while in service in North Africa and Italy observed that sulfonamide light dermatitis accounted for 72.2 per cent of several hundred cases of sulfonamide rashes. Other drugs, such as acriflavine and cocaine, can reactivate a sulfonamide light dermatitis. In most cases the lesions subside within a few days. Dark-

skinned individuals are less likely to develop this complication. The drug need not be discontinued, but all patients should be given appropriate instructions for the avoidance of sunlight.

Conjunctivitis commonly occurs when sulfathiazole is given, and is sometimes accompanied by scleritis, or by fever or skin eruptions.

Some degree of leucopenia often appears during sulfonamide therapy and should be checked by frequent white blood cell counts in order to forestall the more serious forms. About 250 cases of granulocytopenia or agranulocytosis from sulfonamide compounds have been reported in the literature (Long¹¹⁷⁴), and with few exceptions occur after the twelfth day of treatment, most frequently between the seventeenth and twenty-fifth days, but as late as the seventieth day. It follows the administration of sulfanilamide and sulfapyridine more often than the others. This constitutes one of the most serious complications with a high mortality rate, and is an indication for the immediate withdrawal of the drug. In a few cases, leucemoid reactions, characterized by numerous immature granulocytes, appear, but apparently result in no harm to the patient.

A slowly progressive or, more rarely, an acute hemolytic anemia may occur during sulfonamide therapy, with all the usual evidences of increased erythrocyte destruction and increased fragility. While the milder forms may represent a direct pharmacologic effect of the drugs, the sudden onset of the acute type, often after small or initial doses of a second course, and its frequently accompanying fever suggest a hypersensitive reaction. It usually appears in the first days of treatment, and more often from sulfanilamide and sulfapyridine than the others. Oliguria or anuria may result from injury to the tubular epithelium and from precipitation of acid hematin crystals in the renal tubules.

Thrombocytopenic purpura due to sulfadiazine in children has been reported by Meyer,¹¹⁷⁷ Koteen,¹¹⁷⁸ and several others, and to sulfathiazole by Strong and Glassburn.¹¹⁷⁹

¹¹⁶⁷ JOHNSON, R. D. *J. A. M. A.* 124: 979, 1944

¹¹⁶⁸ FREEMAN, H. E. *Arch. Dermat. & Syph.* 48: 15, 1944

¹¹⁶⁹ DIRECTOR, W. *Ibid.* 48: 523, 1943

¹¹⁷⁰ GREENBERG, S. I., and MESSER, A. L. *J. A. M. A.* 122, 944, 1943

¹¹⁷¹ DARDINSKI, V. *J. Am. J. Clin. Path.* 13: 75, 1945

¹¹⁷² RAFFIELLO, J. F., and NICHOLS, S. *J. Pediat.* 20: 753, 1942

¹¹⁷³ KASSELBERG, L. A. *J. A. M. A.* 123: 1035, 1943

¹¹⁷⁴ BLUM, H. F. *J. Invest. Dermat.* 4: 1-9, 1941

¹¹⁷⁵ PARK, R. G., and PLATTS, W. M. *Brit. M. J.* 2: 36, 1942

¹¹⁷⁶ PETERKIN, G. A. G. *Brit. M. J.* 2: 1, 1945

¹¹⁷⁷ MEYER, A. H. *California & Western Med.* 60: 99, 1944

¹¹⁷⁸ KOTEEN, P. J. *A. M. A.* 126: 835, 1944

¹¹⁷⁹ STRONG, P. S., and GLASSBURN, E. M. *Ann. Int. Med.* 23: 237, 1945

Such cases often exhibit hepatosplenomegaly, lymphadenopathy, and fever, and often terminate fatally. However, an increase in the platelet count usually occurs during sulfonamide therapy (Kracke and Townsend¹¹⁷⁹). Williams¹¹⁸⁰ detected 9 instances of hepatosplenomegaly among 1,000 cases treated with sulfapyridine.

Fever is a common manifestation of sulfonamide sensitivity. First¹¹⁸¹ noted it in 71 cases among 186 reactions. It usually appears between the fourth and fifteenth days of treatment or later though often within the first nine days (Kent and Diefendorf¹¹⁷⁷), is sudden in onset, intermittent in character and high in degree (sometimes up to 106 or 107 F), and disappears rapidly when the drug is discontinued. Bradycardia is a constant feature. Decided chills may be caused by renewed administration of even small doses, and along with the fever leucocytosis, and accelerated blood sedimentation may simulate septic conditions, confusing the diagnosis. Lyons and Balberor¹¹⁸² called attention to the occurrence of high fever in a considerable percentage of patients 7 days after the readministration of sulfathiazole. Dowling and Lepper¹¹⁸³ found drug fever to be about three times more likely in the second course of treatment than in the first, and following sulfathiazole more often than sulfadiazine or sulfapyridine. Fever may often be associated with skin eruptions, polyarthritides, arthralgias, peripheral neuritis, splenomegaly, and interstitial myocarditis. Moeschlin¹¹⁸⁴ reporting 6 cases of drug fever due to sulfathiazole, observed that it is sometimes accompanied by corneal infiltration, marginal phlyctenae, and glossitis, all of short duration. When fever is caused by one sulfonamide, it is occasionally possible to substitute another safely, if such therapy is urgent.

Approximately 100 cases of polyneuritis following sulfonamide therapy have been reported, according to Mueller,¹¹⁸⁵ who added

an additional 7 instances. It is particularly likely to occur after methylated preparations. The lower extremities were more frequently involved than the upper and cranial nerve signs were rare. The condition appeared in several cases within a few days of the start of a second course of therapy. Four patients also had moderate blood eosinophilia. Although polyneuritis may sometimes be the result of toxic damage of nerve tissue, Mueller believes that more frequently it is a manifestation of an allergic reaction.

Asthma due to sulfonamides is relatively rare, but has been reported by Randolph and Rawling¹¹⁸⁶ and Zanfagna¹¹⁸⁷. In one case, use of sulfathiazole containing nose drops for 7 days appeared to be responsible for severe status asthmaticus. Randolph and Rawling¹¹⁸⁶ noted an initial diminution in the eosinophil count during the stage of reactive symptoms in 3 sensitive patients following a single dose of sulfonamide, with a return to relatively high levels 24 to 48 hours after ingestion. Zanfagna's case had giant urticaria, angioneurotic edema, and conjunctivitis, in addition to asthma and a positive passive transfer test was obtained.

Hepatitis with jaundice may follow ingestion of any of the sulfonamides, particularly sulfanilamide. Other manifestations of sensitivity (eruptions, fever, granulocytopenia) may be present at the same time. Differentiation from jaundice due to increased hemolysis can be made by appropriate laboratory methods. Hepatitis may occur at any time during treatment, but usually after at least two weeks. Two cases of acute diffuse hepatic necrosis resulting from sulfadiazine therapy were reported by Herbut and Scanciaciotto¹¹⁸⁸.

Aside from the renal obstruction due to the mechanical effects of precipitated drug crystals, already mentioned, there may rarely ensue a form of nephrosis or nephritis with hyposthenuria or anuria and the appearance of albumin, casts and erythrocytes in the urine. Since it is often accompanied by fever

¹¹⁷⁹ KRACKE R. R. and TOWNSEND E. W. J. A. M. A. 122: 168 1943.

¹¹⁸⁰ WILLIAMS H. V. Lancet 1: 103 1943.

¹¹⁸¹ FIRST I. F. War Med. 5: 150 1944.

¹¹⁸² LYONS R. H. and BALBEROR H. J. A. M. A. 118: 933 1942.

¹¹⁸³ DOWLING H. F. and LEPPER N. H. Am. J. M. Sc. 207: 349 1944.

¹¹⁸⁴ MOESCHLIN S. Schweiz. med. Wchnschr. 72: 505 1942.

¹¹⁸⁵ MUELLER R. Acta med. Scandinav. 121: 93 1943.

¹¹⁸⁶ RANDOLPH T. G. and RAWLING F. F. A. J. A. M. A. 126: 166 1944.

¹¹⁸⁷ ZANFAGNA P. E. Bull. U. S. Army M. Dept. No. 84 p. 117 Jan. 1945.

¹¹⁸⁸ HERBUT P. A. and SCANCACIOTTO T. M. Arch. Path. 40: 94 1945.

and skin eruptions, and since ureteral irrigations and necropsy have in such cases failed to reveal evidence of crystallization or intratubular concretions (Peters and Koven,¹¹⁹³ Black-Schaffer¹¹⁶⁶), it is thought to represent a hypersensitive reaction of the renal parenchyma, particularly the tubules. It may be produced by sulfathiazole, and less frequently by sulfapyridine, sulfadiazine, and sulfamerazine. Permanent renal damage has been noted.

The relationship of the sulfonamides to periarteritis nodosa will be considered in chapter XXIX.

Although oral penicillin therapy has not as yet been extensively employed, the fact that it can cause skin manifestations is shown by reports of a maculopapular rash along with nitrogen retention (Finland et al.¹¹⁹⁰) and of a mild generalized urticaria (Bunn et al.¹¹⁹¹).

As an unusual example of an ingestant drug may be mentioned Markow's report¹¹⁹² of an urticaria developing immediately after amalgam had been used in filling a tooth. Exacerbation of symptoms occurred on removal of the filling and on spilling of the amalgam in the mouth. A positive reaction to contact with mercury was elicited. Complete relief followed removal of all mercury-containing fillings.

Fever is a frequent symptom in drug allergy. This is especially noteworthy because fever is rarely encountered in allergic diseases—with the exception, of course, of serum sickness. The temperature is sometimes as high as 104 to 106 F. (40 to 41.1 C). and, strangely enough, is especially high when the condition is due to antipyretics. As noted above, the sulfonamides are often responsible for drug fever.

It does not appear to be definitely known as yet whether granulocytopenia and agranulocytosis are to be regarded as forms of drug allergy or drug intoxication. Although these conditions are almost certainly to be considered as manifestations of toxicity when

they appear following the use of dinitrophenol (which was once used in the treatment of obesity), the experiments of Madison and Squier¹¹⁹² would indicate that they are truly allergic when they appear following the use of aminopyrine. In a case of agranulocytosis due to aminopyrine in rectal suppositories, Urbach and Goldburgh¹¹⁹⁷ suggested that the allergization was based on a hapten mechanism, the drug conjugating with breakdown products (proteoses and peptones) of the rapid destruction of protein incident to the marked weight loss resulting from the patient's inability to eat. Sulzberger¹ pointed out the same drugs which are likely to cause fixed eruptions, as given in a compilation by Abramowitz and Noun,¹¹²⁷ also may produce granulocytopenia in other patients, as indicated in a list presented by Kracke.¹¹⁹⁴

No drug is free from sensitizing properties, although there is considerable variation among drugs in this respect. There is a range from those that allergize few if any users, such as cascara sagrada, to those that sensitize almost 100 per cent of all persons exposed. Nirvanol, a hypnotic, which was formerly widely used in the treatment of chorea, is perhaps the best example of the latter type: all individuals to whom it was administered in therapeutic doses developed rashes and showed symptoms almost identical with those of serum sickness (Madden¹¹⁹⁵). Not infrequently a state of hypersensitiveness seems to be created by intermittent administration, so that repetition of a small dose, following a long free interval, produces a skin eruption that did not occur after the first course of treatment with the drug. Interestingly, the closely related dilantin (phenytoin sodium) elicits allergic reactions in only 5 per cent of patients.

McArthur, Rawson, and Means^{1196a} reviewed the chemical factors rendering a drug capable of inducing hypersensitiveness, and suggested, on the basis of circumstantial evidence that the capacity to bind proteins and possibly to blockade enzymes is the common chemical factor responsible both for the anaphylactic-like complications of chemotherapy and for the therapeutic effect. This

¹¹⁹³ PETERS, J., and KOVEN, A. J. Ann. Allergy 2: 230, 1944.

¹¹⁹⁰ FINLAND, M., MEANS, M., and ORY, E. M. J. A. M. A. 129: 313, 1945.

¹¹⁹¹ BUNN, P. A., McDERMOTT, W., HADLEY, S. J., and CARTER, A. C. Ibid. 129: 320, 1945.

¹¹⁹² MARKOW, H. New York State J. Med. 43: 1645, 1943.

¹¹⁹³ MADISON, F. W., and SOCIER, T. L. J. A. M. A. 102: 755, 1934.

¹¹⁹⁴ KRACKE, R. R. Ibid. 111: 1253, 1935.

¹¹⁹⁵ MADDEN, J. F. Arch. Dermat. & Syph. 26: 1065, 1932.

mechanism would appear to apply to sulfonamides, thiouracil, arspenamines, and other drugs

Elsewhere we have presented a detailed discussion of the fact that the hypersensitivity is occasionally highly specific, while in other cases there is evidence of group hypersensitivity. Thus Urbach²⁶³ has reported that individuals who are allergic to resorcin occasionally react to the isomeric compounds, pyrocatechin and hydroquinone. A patient of Nathan and Stern's,¹¹⁹⁶ on the other hand, responded only to the resorcin itself.

It cannot be denied that, generally speaking, the treatment of drug allergy still leaves very much to be desired. The only absolutely certain and successful method is that of avoidance of the given substance. In some rare instances success has been achieved by means of skeptophylactic preliminary administrations (see p 216) or by means of the so called "rush" deallergization method (see p 214).

In cases of sulfonamide hypersensitivity substitution of another derivative should be considered, provided such therapy is indicated and penicillin is either not effective (as in bacillary dysentery, lymphogranuloma venereum, and chancroid) or not tolerated. It should not be attempted in the more serious types of reactions, such as agranulocytosis or thrombocytopenia, but may be cautiously tried in the milder forms. In this connection, Park¹¹⁹⁷ found that most patients react only to the single sulfonamide to which they are originally sensitized, but that if a patient is hypersensitive to two, he is probably sensitive to all, as well as sulphanilic acid.

Park¹¹⁹⁷ found hyposensitization to sulfonamides to be consistently successful. The drug is administered orally in four or five di-

vided doses, beginning with an amount too small to cause a reaction (usually 0.1 Gm), and doubling the dose daily until a mild reaction occurs. It is then continued at that level until the symptoms subside and then again increased gradually until 1 Gm is reached (generally in four or five days). About six weeks treatment is necessary. Although one case was again found sensitive when rechecked a year later, he was much less so than before treatment. Park suggests that if hyposensitization is deferred for a time, the benefit may be permanent. Tate and Klorfajn⁷⁸⁶ also reported considerable success in the oral hyposensitization of 30 cases of sulfonamide dermatitis. It is necessary to wait until the original eruption has disappeared, and the patient should avoid sunlight. Continuous blood studies are essential. A preliminary oral test dose of 0.125 Gm is administered twice daily, and if no eruption ensues, is very gradually increased to 2 Gm, repeated at 4 hour intervals. Treatment is continued for at least 14 days. No case appeared to be resensitized. Among the untoward effects noted were fever, aggravation of the dermatitis, and loss of consciousness in one case, and urticaria in two. McCormick¹¹⁹⁸ pointed out that vitamin C deficiency may be the conditioning factor which predetermines potential sensitivity to the sulfonamides. The avitaminosis may be precipitated by increased vitamin demands due to the existing infection or to the toxic effects of the drug. He suggests determination of vitamin C in the urine prior to sulfonamide therapy and, if deficiency is found, large doses of ascorbic acid. Several of his cases of sulfonamide sensitivity responded favorably to this treatment. Nicotinic acid has been suggested as having much the same effect.

¹¹⁹⁶ NATHAN E., and STERN F. *Dermat Wechschr* 91: 1471-1630
¹¹⁹⁷ PARK R. G. *Lancet* 1: 401 1944 *Brit M J* 1: 781-816 1944

¹¹⁹⁸ MCCORMICK W. J. *Canad M A J* 52: 68 1945

CHAPTER XV

INJECTANTS

THIS group comprises all the antigenic substances that allergize the organism by way of the parenteral route, and that, when reinjected, elicit manifestations of hypersensitiveness. We must include here, therefore, all drugs that are administered by subcutaneous, intramuscular, or intravenous injection, as well as hormones and vitamins. Foreign serums, particularly antitoxic serums, constitute an important group of injectants. Finally, the bites and stings of insects will be considered

A. DRUGS

The allergic manifestations brought on by the parenteral administration of drugs do not differ in principle from responses to the same drugs administered orally, except for the fact that they are, as a rule, more severe and of longer duration. Therefore, the reader is referred to the section on allergy to sulfonamides, alkaloids, arsenic, barbiturates, bromides, iodides, digitalis, and mercury (p. 316). Here we shall consider only hypersensitiveness to penicillin, arsenicals, diodrast, gold, and local anesthetic agents—for the reason that these drugs are almost invariably administered parenterally—and hypersensitiveness to bismuth when given by injection.

1. PENICILLIN

Penicillin may exert an allergenic effect by injection, by ingestion, or by contact. The last-named type of exposure will be considered in the next chapter, while orally administered penicillin was mentioned in the last chapter. On the whole, allergic reactions to this drug, unlike the sulfonamides, are not too common, and serious manifestations are rather rare.

Lyons¹²⁹⁹ reported 12 cases of urticaria among 209 patients treated, Keefer et al.¹³⁰⁰ 14 cases among 500 treated, and Flinn et al.¹³⁰¹

an incidence of 3 per cent of mild, transient urticaria. Single instances of giant urticaria have been observed by Criepe¹²⁹² and Barker.¹²⁹³ Urticaria is undoubtedly the most common complication. It may occur at any stage of the treatment, and even several days after treatment is discontinued. It usually responds to epinephrine or ephedrine, and rarely persists more than a few days, although it has been known to last for as long as four weeks. Since the urticaria is not infrequently accompanied by fever (if the patient was originally afebrile, or higher temperatures in febrile cases), angioneurotic edema of the face and hands, arthralgias especially of the smaller joints, and occasionally lymphadenopathy or abdominal pain, the resulting clinical picture may simulate that of serum sickness. Fever does not usually occur unless the urticaria is severe, and is rarely of high degree, but may sometimes appear without urticaria in the first days of treatment. A marked blood eosinophilia is occasionally noted, with or without the other findings being present. The observations that the course of the urticaria is independent of continuation or cessation of treatment and that subsequent courses of penicillin are no more likely to give rise to recurrent urticaria (Lyons¹²⁹⁹) were not confirmed by Criepe,¹²⁹² whose case developed massive generalized urticaria after the first injection of the second course, nor in the experience of the authors.

Bullous or vesicular dermatitides due to intramuscular injections of penicillin were described by Morris and Downing,¹²⁹⁴ Lamb,¹²⁹⁵ and Cohen and Pfaff.¹²⁹⁶ Fever and toxic symptoms were present in some cases. Canizares¹²⁹⁷ patient demonstrated photosensitivity believed due to the same cause, manifesting a morbilliform eruption on sunburned

¹²⁹⁹ LYONS, C. J. *J. A. M. A.* 123:1007, 1943.

¹³⁰⁰ KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., JR., LOCKWOOD, J. S., and WOOD, W. B., JR. *ibid.* 123:1215, 1943.

¹³⁰¹ FLINN, L. B., MCGEE, L. C., FRATERSTON, W. P., and KERN, D. O. *Delaware State M. J.* 17: 133, 1945.

¹²⁹² CRIEPE, L. H. *J. A. M. A.* 126: 429, 1944.

¹²⁹³ BARKER, A. N. *Lancet* 1: 171, 1945.

¹²⁹⁴ MORRIS, G. E., and DOWNING, J. G. *J. A. M. A.* 127:711, 1945.

¹²⁹⁵ LAMB, J. H. *Arch. Dermat. & Syph.* 52: 93, 1945.

¹²⁹⁶ COHEN, M. T., and PFAFF, R. O. *ibid.* 51: 172, 1945.

¹²⁹⁷ CANIZARES, O. *ibid.* 52: 17, 1945.

areas four days after penicillin treatment. Asthma of alarming severity beginning more than two days after the end of a course of 2,400,000 units of penicillin for the treatment of syphilis accompanied by giant urticaria fever, generalized adenopathy and severe systemic symptoms and persisting for four days was reported by Price and his co-workers.¹⁷⁰⁸ A case observed by Service¹⁷⁰⁹ exhibited following the acute complaints of urticaria nearly generalized edema including laryngeal vomiting and bursitis a late reaction characterized by recurrent severe migraine ultimately controlled by intravenous niacin (nicotinic acid).

Aside from the cases of allergic contact dermatitis not considered here, skin tests by any method are almost uniformly negative, although the junior author has seen two positive intracutaneous reactions (one of which was regularly accompanied by "satellite" wheals on the proximal portions of the same extremity) and one positive scratch patch test. In Crip's case positive intradermal passive transfer, and precipitin tests were obtained, although no anaphylactic antibodies were demonstrated. Barker elicited positive scratch and intracutaneous tests in his case while Flinn's patient gave positive intradermal reactions only to certain brands of manufacture. A case studied by Zeller¹²¹⁰ indicated that not only the urticarial response to intramuscular injections of penicillin but also the positive intradermal and passive transfer tests may be temporary. Fernberg¹²¹¹ showed that patients sensitive to extracts of *Penicillium* spores do not react to the drug penicillin, although false positive reactions were obtained even in normal subjects, if too great a concentration was used. Among 144 previously unexposed persons Rostenberg and Welch¹²¹² found that approximately 55 per cent exhibited a delayed tuberculin type reaction to the initial intracutaneous injection of 1,000 units of crystalline penicillin sodium, appearing several hours later, becoming maxi-

mal in twenty four to forty eight hours and consisting of erythema and edema. The significance of these reactions is not known. Passive transfer tests were consistently negative. Repeated multiple injections caused in some persons an Arthus type of reaction—transient wheal-like responses eventually changing into a tuberculin type. In one of their subjects who had no prior exposure to penicillin but who had worked with a variety of molds for years patch tests were positive but only at the site of previous positive intracutaneous tests with penicillin sodium while precipitin and passive transfer tests were negative (Welch and Rostenberg¹²¹³).

McClosky and Smith¹²¹⁴ demonstrated by anaphylaxis and the Schultz Dale technic that guinea pigs can be sensitized to commercial penicillin although positive reactions are often atypical or delayed. They suggest that the penicillin antigen antibody combination lacks permanency and is more readily reversible than with true proteins.

It is important that true sensitivity to penicillin be distinguished from that to contaminants carried over from the culture medium (corn extract, corn steep liquor, etc.) in the processing. It has been suggested that refinements in manufacture will further eliminate impurities so that reactions may be expected to be less frequent in the future. Experience to date would seem to have already confirmed this in part. It has also been noted that certain batches of the drug appear to produce reactions more frequently than others. Patients who react to one preparation will sometimes tolerate that of a different manufacturer.

In dealing with so potent an antibiotic other mechanisms of the production of untoward reactions must be considered. The possibility of a Jarisch Herxheimer type of reaction was suggested by Graves Carpenter, and Unanue¹²¹⁵ who reported two cases of vesicular eruptions following penicillin treatment in patients with chronic infections antecedent dyshidrosis and positive reactions to trichophyton. They attribute the dyshidrosiform

¹⁷⁰⁸ PRICE D E, McNAIRY D J and WHITE E L J A M A 128 183 1945

¹⁷⁰⁹ SERVICE W C Letters Internat Corr Club of Allergy Series 8 77 1945

¹²¹⁰ ZELLER M Ann Allergy 3 360 1945

¹²¹¹ FERNBERG S M J Allergy 15 271 1944

¹²¹² ROSTENBERG A Jr and WELCH H Am J M Sc 210 158 1945

¹²¹³ WELCH H and ROSTENBERG A Jr J A M A 126 10 1944

¹²¹⁴ MCCLOSKEY W T and SMITH M I Proc Soc Exper Biol & Med 57 2 0 1944

¹²¹⁵ GRAVES W N, CARPENTER C C and UNANUE R W Arch Dermat & Syph 50 6 1944

lesions to a disturbance of normal immunologic balance and the liberation from foci of infection of excess quantities of toxins to which the patient is sensitive. This concept is not far removed from Milian's hypothesis of biotritopism (see below) Herpes labialis and progenitalis which occasionally complicate the course of penicillin therapy may be due to the same mechanism. True Herxheimer reactions frequently occur in penicillin-treated cases of syphilis.

There is no evidence that other untoward effects of penicillin, such as pain at the injection site, headache, flushing, faintness, unpleasant taste sensations, muscle cramps, tingling in the testes, mild gastro-intestinal symptoms, and thrombophlebitis following intravenous administration, are on an allergic basis.

Little is as yet known about the allergenic potentialities of the other antibiotics. However, apparent sensitization to streptomycin was noted by Hinshaw and Feldman^{127a} in four patients following the first doses of a second course of the drug. The symptoms consisted of violent febrile reactions. Hyposensitization permitted continuation of treatment without ill effects.

2. ARSENICALS

To begin with, it must be stressed that hypersensitiveness to the arsphenamines and mapharsen is by no means identical with sensitivity to arsenic. Thus, a patient who is allergic to arsphenamine may be hypersensitive only to trivalent organic arsenic compounds, and can therefore tolerate a pentavalent organic arsenical, such as tryparsamide, or inorganic arsenic, such as Fowler's solution. In other cases, however, the hypersensitiveness may relate to every arsenic compound (Pillsbury^{127b}).

Because of their frequency and clinical importance, the manifestations of allergy to the arsphenamines merit description in some detail. They may be divided into six principal groups: (1) immediate exanthems with fever; (2) "erythema of the ninth day," (3) fixed skin eruptions; (4) late dermatitides; (5)

nitritoid crisis; and (6) constitutional symptoms. Naturally it is not always possible to draw such sharp distinctions, for the symptoms of the various groups sometimes appear simultaneously or in succession.

(1) When massive dose chemotherapy by the intravenous drip method is employed in early syphilis, immediate eruptions appear in 52 per cent of the cases, according to Hyman, Chargin, and their associates^{127c}; these eruptions are scarlatiniform, morbilliform, or erythema-multiforme-like in character and are usually associated with fever.

(2) Not infrequently acute universal exanthems appear between the seventh and the tenth day—most commonly on the ninth day—following the second or third arsphenamine injection. Milian¹²⁷ coined the term "erythema of the ninth day" to designate these manifestations. Peters^{127d} reported 54 cases of this syndrome with an abrupt onset between the fifth and nineteenth days after the last injection characterized by malaise, chills, fever, anorexia, nausea, vomiting, generalized aching, headache, and sore throat. This was followed one day later by a generalized eruption variously described as morbilliform, scarlatiniform, blotchy, or macular erythematous, erythema-multiforme-like, and rarely urticarial. Lymphadenopathy was commonly encountered, and hepatomegaly, splenomegaly, and jaundice in a few cases. The average duration was six days and there were no fatalities. Leifer^{127e} holds that the safest course is to consider any febrile episode (except the Herxheimer reaction), especially in the first three weeks of arsenotherapy, a probable manifestation of sensitivity to arsenic, and this is particularly true when the entire syndrome of erythema of the ninth day is present. It appears also to apply with equal force to those cases in which no rash is detected.

Although the existence of this clinical entity is now generally accepted, its pathogenesis is still a moot question. Milian is of the opinion that ninth-day erythema is an expression of so-called biotritopism. By this he means the activation of latent micro-organisms within the human organism, regardless of

^{127a} HINSHAW, H. C., and FELDMAN, W. R. *Proc. Staff Meet., Mayo Clin.*, 28, 313, 1943.

^{127b} PILLSBURY, D. M. *Arch. Dermat. & Syph.*, 34, 103, 1936.

^{127c} HYMAN, H. T., CHARGIN, L., RICE, J. L., and LEIFER, W. *J. A. M. A.* 113, 1203, 1939.

^{127d} PETERS, E. E. *Am. J. Syph., Gonorr. & Ven. Dis.* 25, 527, 1941.

^{127e} LEIFER, W. *Am. J. M. Sc.* 210, 438, 1945.

whether this sudden increase in virulence is evoked by chemotherapy by physicochemical influences (cold heat or light) or by intercurrent acute infections. He holds therefore that the symptoms that manifest themselves at about the ninth day following the administration of various drugs—rubeolalike morbilliform (FIG 148) or scarlatiniform exanthems with fever headache vomiting angina and lymphadenopathy—are in effect mild manifestations of actual rubeola or measles or scarlet fever—in short genuine infectious diseases.

Together with many other authors the present writers reject Miha's concept. We emphatically do not believe that these exan-

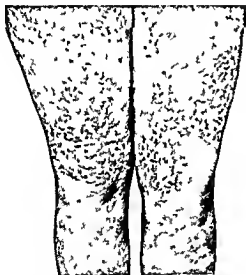


FIG 148 MORBILLIFORM EXANTHEM APPEARING ABOUT NINTH DAY AFTER ADMINISTRATION OF NEOARSPHENAMINE

thems are to be regarded as the expression of any so called biotropism for patients presenting the ninth day exanthems almost invariably give positive reactions to intracutaneous tests with arsphenamine. Further more Schreiner and Ensbrunner¹²¹⁹ succeeded in transferring the hypersensitiveness passively by means of blood serum or vesicle content in 5 of 8 cases. The argument in favor of the theory of the allergic character of the ninth day exanthem finds further strong support in the experimental investigations of Frei of Nathan and Munk and of others.

They demonstrated that intracutaneous injections of minute amounts of neoarsphenamine and other drugs can bring about allergization of the entire skin in human beings in about ten days. We therefore regard the ninth day erythema as an allergic manifestation corresponding to that of serum sickness. On the other hand it is true that treatment with arsenicals may often be continued in such cases after a period of at least one month provided due caution is taken although some patients will exhibit reactions. The reason for the apparently permanent protection against recurrence that may follow erythema of the ninth day awaits elucidation. It must be pointed out however that in all of 14 cases observed by Leifer^{1215a} early continuation of mapharsen therapy after the initial reaction led to serious parenchymatous damage in the form of jaundice and agranulocytosis with or without nephritis.

(3) The fixed arsphenamine eruptions (FIG 149) are in every respect similar to those just described as resulting from hypersensitivity to antipyrine and other drugs. It is noteworthy in this connection that Chagnon and Leifer¹²¹⁸ Sulzberger⁴ and Abramowitz and Russo¹²¹⁹ observed that fixed drug eruptions due to neoarsphenamine were non-specifically activated by injections of his muth. The writers are of the opinion that this can be explained on the basis of metal lergy (p. 28).

(4) Less frequently observed are the late arsphenamine dermatitides. They develop somewhere near the middle or toward the end of the first or second series of injections. At first there is itching then erythema appears especially on the flanks and extremities. These eruptions not infrequently develop into erythrodermas (FIG 150) or exfoliative dermatitides (FIG 151). Patients with arsphenamine dermatitis may present such eye complications as panophthalmitis superficial keratitis corneal edema and conjunctivitis the allergic nature of the inflammation being indicated by the extreme eosinophilia demonstrable in the conjunctival secretion (von Pastinszky¹²²⁰). The vesiculobullous and exfoliative dermatitides are among the most

1219 SCHREINER K. and ENSBRUNNER G. *Arch. f. Dermat. u. Syph.* 10: 61, 1934.

* PASTINSZKY S. *von Acta dermat. u. syph.* 24: 457, 1944.

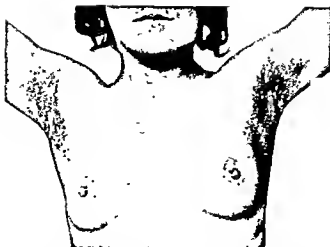


FIG 149 FIXED DERMATITIS OF AXILLAE APPEARING AFTER EACH INJECTION OF NEOARSPHENAMINE



FIG 150 ERYTHRODERMA DUE TO HYPERSENSITIVENESS TO ARSPHENAMINE

serious of reactions to the arsenicals, and if the patient recovers, no attempt should be made to resume this type of therapy

Cases of arsphenamine dermatitis are characterized by positive reactions to epidermal

skin tests with arsphenamine. In 3 of 6 cases, Schreiner was able to demonstrate the presence of a specific hypersensitivity by means of the passive transfer test. Ensbrunner recommended skin tests by means of the intracutaneous injection of 0.02 cc. of a 1:1000 solution of neoarsphenamine dissolved in physiologic salt solution and epidermal application of 10 per cent neoarsphenamine. Robinson²²⁸ found the intradermal technic of no value, but patch tests with a 30 per cent solution of neoarsphenamine and 4 to 6 per cent mapharsen read in 48 to 72 hours may be significant if strongly positive

The treatment of arsenical dermatitis consists of large quantities of sugar by mouth and dextrose by vein, calcium compounds intravenously, and large doses of ascorbic acid and thiamin chloride. In urticarial types, change to another brand or injections of epinephrine may be adequate to control the condition

Once an individual has suffered from an arsenical dermatitis, the condition can be made to flare up by agency of other factors, such as other drugs, particularly bismuth or mercury, and also bacterial or mycotic infections (Stokes and Kulchar²²⁹). The mechanism underlying this phenomenon is discussed in some detail on page 66

The question as to whether the course of treatment may be continued in the case of patients who have manifested the above mentioned reactions is, naturally, of very great importance. It is probably advisable, as

mentioned above not to resume therapy with arsenicals in any case who has exhibited a vesiculobullous or exfoliative eruption although penicillin may almost always and heavy metals may often be employed safely. In milder types such as a fleeting scarlatiniform or morbilliform rash with some pruritus or the fixed eruptions if treatment is deemed necessary change to another arsenical for example mapharsen if this is not the offending drug may be undertaken cautiously. If this also precipitates the eruption treatment should be immediately interrupted. Skin tests unfortunately are of scant significance in this connection. Cannon and Karelitz¹ Robinson¹⁹⁹² Beerman¹⁹⁹³ and others have

increased with successive doses of 0.06 0.12 0.24 0.4 0.6 Gm etc. If mapharsen is the drug of choice initial tests may be performed with 0.004 to 0.006 Gm and subsequent doses if tolerated could be 0.008 0.016 0.032 and 0.06 Gm.

Brief consideration must be given here to prophylaxis against arsphenamine dermatitis. Klauder was the first to call attention to the fact that one of the principal causes of this dermatitis is faulty venipuncture leading to perivenous injection of the drug. The subsequent damage to the tissue most probably evokes formation of a conjugate protein antigen formed by the union of the drug and the damaged tissue that allergizes the organism.



FIG 131 GENERALIZED EXFOLIATIVE DERMATITIS FROM ARSPHENAMINE INJECTIONS

shown that very little if any information can be gathered from either positive or negative results of patch scratch or intracutaneous tests. Robinson⁷ found that only the intravenous test was of any value. However this test may not be employed until at least three months after the disappearance of all symptoms—and then only with a preparation that has been found to elicit no reaction when applied in a patch test. If an intravenous injection of 0.03 to 0.06 Gm of neoarsphenamine or arsphenamine causes itching or erythema further treatment is contra-indicated. Otherwise the dosage may be cautiously in-

creased on the basis of experiments showing that animals can be protected by intracardiac injections following cutaneous sensitization by an arsphenamine. Sulzberger rightly suggested that in any case in which leakage occurs about a vein during an arsphenamine injection a determined effort should be made to complete the intravenous injection (by entering some other vein) in order to protect the patient against the development of hypersensitivity.

Another approach to this problem was pioneered by Sulzberger and Oser²⁶⁹ who reported that administration of ascorbic acid influenced the experimental sensitization of guinea pigs to arsphenamine. Dainoff²⁵ and Corna⁷¹ reported that patients with previous arsphenamine dermatitis with positive patch tests were subsequently able to tolerate more

CANNON A B and KARELITZ M B A b Dermat & Syph
29 45 1934

ROBINSON H M South M J 27 515 1933

BEERMAN H Penn yl an a M J 39 600 1936

of the same arsenical without further reaction, if massive doses of vitamin C were first given intravenously, followed by a high maintenance dose by mouth. However, a number of authors have not been able to obtain such satisfactory results. More recently, Abt,²⁵³ and also Bundesen and his associates,²⁵⁴ developed a method for detecting cases in which ascorbic acid will make possible the continuation of treatment with this drug. If the drug fails to elicit a positive patch test reaction when mixed with 10 per cent ascorbic acid, they consider simultaneous courses of antiluetic and ascorbic acid therapy of value. It is interesting to note that under this regimen the reactions to patch tests become markedly attenuated and even negative.

(5) Frequently after intravenous injections—and also, although only exceptionally, after intramuscular injections—there appears a symptom complex that Milian²⁵⁵ called “nitritoid crisis” because its symptoms are similar to those following administration of amyl nitrite. A sudden onset, during or immediately following the injection, is characteristic of this condition. Subjective symptoms may precede the clinical manifestations: the patients frequently say afterward that they suddenly felt a “strong rush of blood to the head,” combined with a flush and a feeling of pressure in the head, as well as vertigo and tinnitus aurium. In addition, “burning” in the mouth, pain in the gums, a sensation as though the tongue and the gums were swelling, and occasionally a tickling sensation in the extremities are reported. Objectively this syndrome begins with a reddish-blue to bluish-purple discoloration of the face, probably attributable to a toxic vasodilation. Because of these symptoms, it is referred to abroad as the “angioneurotic symptom complex”—not to be confused with angioneurotic edema.

As a rule, these alarming symptoms subside rather quickly. Not altogether infrequently, however, they are followed by swelling, commonly of the lips and eyelids, but sometimes involving the entire face. This edema may occur not only in the skin, but also in the mucosa of the mouth, throat, and respiratory

tract, either simultaneously or independently. Abdominal cramps, diarrhea, rheumatoid complaints, amauroses, and other symptoms occasionally appearing in association with the above named findings might well be due to the same cause. It is only in extremely rare cases that nitritoid crises develop so rapidly and become so intense as to result in death.

There is a considerable divergence of opinion as to the pathogenesis of this often highly alarming syndrome. Some authors implicate physicochemical changes in the blood colloids, brought on by the injected drug: in other words, they postulate the presence of a hemoclastic crisis (see p. 38). This view is supported by the fact that a similar condition can be produced experimentally by intravenous injection of colloidal solutions (e.g., India ink), and by the fact that the severity of the response is in direct proportion to the size of the colloidal particles in the injected solutions. Other authorities regard the nitritoid crisis as an expression of a reflex from chemotactile stimulation of nerve endings in the walls of the veins. Still another group interprets the condition as an unusual reaction of the sympathetic nervous system. Schreiner, on the other hand, believes the condition to be allergic in character, for he succeeded in passively transferring the hypersensitiveness from patients with this syndrome. The present writers are in complete agreement with this view, since we were able to prevent these crises, in patients known to be prone to them, by skeptophylactic preparatory administration of repeated minute doses of arsphenamine (p. 214).

(6) Finally, mention must be made of various constitutional allergic symptoms that occasionally appear: granulocytopenia, purpura haemorrhagica, neuritis, gastro-intestinal reactions (abdominal pain, diarrhea), and acute cerebral edema. Naturally, it is not always easy to decide, in a given case, whether the manifestations are due to toxicity or to allergy. But that these reactions may at times be of allergic origin must be admitted beyond any question. Thus Landsteiner and Jacobs,³⁹ in animal experiments, succeeded in evoking the same phenomena and, in some instances, even in producing anaphylactic death. Ac-

²⁵³ Abt, A. F.: U. S. Navy. *M. Bull.* 40: 291, 1942.

²⁵⁴ Milian, G.: *Presse méd.* 34: 1313, 1926.

cording to Fingerland¹ the myocardium and kidneys of persons who have died of arsphenamine dermatitis present lesions composed of a diffuse eosinophilic infiltration containing Charcot Leyden crystals and periarterial granulomas consisting of epithelioid and giant cells. Schwartz and VonderHeide¹²⁷ review the reasons which led them to conclude that their case of thrombocytopenic purpura due to mapharsen (oxophenarsine hydrochloride) had many of the characteristics of a hypersensitive reaction and resembled the nitritoid phenomenon. Three cases of acute cerebral edema with apoplectic convulsive and pseudoepileptic manifestations due to neoarsphenamine therapy were reported by Espejo and Voto Bernalles¹²⁸. This grave complication occurred after the third injection in each case and prodromal symptoms consisted of acute headache, vomiting, epigastric pain, diarrhea, insomnia and inability to work. They attribute the condition to a local allergic phenomenon.

3 BISMUTH

Allergy to bismuth is much less frequently encountered than hypersensitivity to the arsenical preparations. The skin manifestations may be erythematous (Fig. 152), eczematous, urticarial, bullous or pruritic. Fixed eruptions as well as exfoliative dermatitides are also occasionally observed. The syndrome of ninth day erythema in association with bismuth therapy was reported by Goldman and Clarke¹²⁹ and by Grund¹³⁰. It is noteworthy that allergy to bismuth is particularly likely to appear when the patient has previously been hypersensitive to arsphenamine (metallergy).

Therapeutically the first thing to do is to make a change in the preparation employed preferably to a soluble one and to try treatment with a smaller dose or lengthen the interval between injections. Tolerance can also be achieved sometimes by means of skeptophy-

lactic intramuscular preparatory injections of minute amounts of bismuth about one and a half hours prior to the injection of the full dose (Sterling).

4 DIODRAST

This is an iodine compound widely used for intravenous urography and other roentgenographic purposes. A severe hemorrhagic erythema multiforme following the first injection of this drug in a patient using iodized salt was observed by the authors. In the last



FIG. 152 LOCAL BISMUTH HYPERSENSITIVENESS AT SITE OF INJECTION.

Note zones of sensitization and desensitization.

few years eight deaths from diodrast attributed to a hypersensitivity to iodine have been reported in the literature (Tachot¹³¹, Crane¹³², Dolan¹³³, Jungnickel¹³⁴, Goldburgh and Baer¹³⁵). Replies to an inquiry by Pendergrass and his associates³⁶ elicited the in-

¹³¹ TACHOT A. J. *d urol* 40: 522, 1933.

¹³² CRANE J. J. *J. Urol* 42: 71, 1939.

¹³³ DOLAN L. P. *J. A. M. A.* 114: 138, 1940.

¹³⁴ JUNGNICKELE G. *Muenchen med. Wchnschr.* 87: 393, 1940.

¹³⁵ GOLDBURGH H. L. and BAER S. *J. A. M. A.* 118: 1051, 1942.

³⁶ PENDERGRASS E. P., CHAMBERLIN G. W., GODFREY E. W. and BURCK E. D. *Am. J. Roentgenol.* 48: 741, 1942.

FINGERLAND A. *Ve handl. d. deu. sch. ps. h. Gesells. h.* 29th sess. on 1937, p. 321.

¹²⁷ SCHWARTZ M. and VONDERHEIDE E. C. *J. A. M. A.* 128: 657, 1945.

¹²⁸ ESPEJO L. D. and VOTO BERNALLES J. *Rev. Neu. o Psiquiat.* 5: 315, 1942.

¹²⁹ GOLDMAN L. and CLARKE G. E. *Am. J. Syph. Gono. & Ven. Ds.* 23: 224, 1939.

¹³⁰ GRUND J. L. *Arch. De. mat. & Syph.* 41: 10: 6, 1940.

information that 20 deaths were attributed to injections of urographic contrast mediums in 661,800 examinations, and 132 instances of anaphylactic shock. Urticarial and erythema-multiforme-like eruptions and numerous other reactions have been noted. Not all of these are indubitable examples of hypersensitivity. In order to detect patients who are allergic to this drug, an intradermal test with 0.05 cc. of diodrast was suggested by Naterman and Robins¹²²⁷. Only 24 per cent of patients with positive skin reactions subsequently had systemic effects when subjected to excretory urography, while 30 per cent of those with constitutional reactions had had negative skin tests (Robins¹²²⁸). Dolan¹²²⁹ considered this method unreliable and recommended placing a quantity of 1 or 2 cc. under the patient's tongue and keeping it there for five minutes. If no untoward symptoms appear, the drug may be swallowed, and if no reaction develops within thirty minutes, the dye may be injected. Unfortunately, even this precautionary measure cannot always be depended upon, as in the case reported by Goldburgh and Baer.¹²³⁰ Archer and Harris¹²³¹ described a simple ophthalmic test in which one drop of the undiluted dye is placed directly on the conjunctiva of one eye, which is then closed for one and a half minutes. It is examined for injection of the conjunctiva and sclera immediately and again in two minutes. When the reaction is of the decided type with engorgement of the vessels from the iris to the periphery, intravenous use of the dye is absolutely *contra-indicated*. Patients with moderate injection usually react to intravenous injection with nausea, vomiting, vasomotor dilatation and occasionally generalized pruritus, urticaria, and slight swelling of the membranes of the upper portion of the respiratory tract, while those with minimal reactions suffer little or no effects.

5 GOLD COMPOUNDS

The allergic skin and general manifestations due to gold compounds are in many respects similar to those observed in arsphenamine

hypersensitivity. Extensive morbilliform and scarlatiniform (Fig 153), intensely pruritic exanthems, ninth-day erythema, exfoliative dermatitis, as well as angioneurotic edema, neuritis, gastro-intestinal reactions, purpura haemorrhagica, and even death following severe anaphylactic shock (e.g., after 0.001 Gm. of krysolgan), have been reported. Far fewer severe phenomena have been observed, however, since massive doses have been replaced

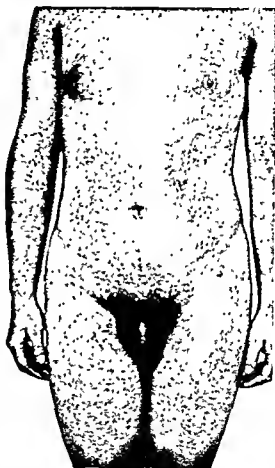


FIG 153 GENERALIZED DERMATITIS AFTER INJECTIONS OF GOLD SODIUM THIOSULFATE

by small amounts in the treatment. To prevent allergization, it is important that the interval between two injections should not be too long (a week at the most). This consideration was advanced by Rothmann, who holds that it applies equally to all injected drugs. Guinea pig experiments and clinical observations convinced Carratala¹²³² that hy-

¹²²⁷ NATERMAN, H. L., and ROBINS, S. A. *J. A. M. A.* 119: 491, 1942

¹²²⁸ ROBINS, S. A. *Am. J. Roentgenol.* 48: 766, 1942

¹²²⁹ ARCHER, V. W., and HARRIS, I. D. *ibid.* 48: 763, 1942

¹²³² CARRATALA, R. E. *For. en Letters, J. A. M. A.* 120: 1331, 1942

persensitiveness to sodium gold thiosulfate is related to hypovitaminosis C and could be prevented by administration of ascorbic acid

6 LOCAL ANESTHETIC AGENTS

The problem of hypersensitiveness to injected local anesthetic agents such as cocaine procaine hydrochloride and their many derivatives is a particularly difficult one since it is often impossible to determine whether untoward effects are due to pharmacologic effects of the drug in large dosage to sensitivity or to the added epinephrine. However there is reason to suspect that certain of these cases are on an allergic basis. These drugs are commonly absorbed from injections into any part of the body or from the spinal canal but absorption and subsequent untoward effects may result from local application to skin or mucous membranes particularly if they are inflamed or abraded from swallowing after application to the nasopharynx epiglottis or esophagus from the urethra or in very rare instances from the rectum or vagina. Drugs of this series may also act as contactants as commonly occurs in dentists physicians workers in pharmaceutical plants and others coming into repeated contact with them or in patients usually following use of an anesthetic ointment. This type of exposure need not concern us here. Contact conjunctivitis pharyngitis proctitis and similar conditions due to local application of anesthetics is occasionally seen and is based on the same mechanism.

Little information is available concerning systemic allergization to local anesthetics. In some cases the untoward effects are due to the epinephrine which is usually included in the solution. In cases of coma following dental anesthesia with procaine and of generalized urticaria due to monocaine the junior author observed positive intracutaneous tests to 0.1 cc of the agents. By performing similar tests with a series of alternative derivatives in the usual therapeutic concentration he was able to select and recommend substitutes which were tolerated without difficulty. However, in most cases skin tests are not as reliable, and they certainly will have no relationship to possible toxic effects. It has been suggested that in cases of suspected sensi-

tivity to spinal anesthesia a preliminary test be conducted by producing skin wheals with 1 cc of a 1 per cent solution of procaine hydrochloride without epinephrine and with the same amount of isotonic solution of sodium chloride. The patient is observed not only for local differences between the wheals but also for systemic reactions such as dyspnea apprehension rapid pulse and fall in blood pressure. A local reaction particularly erythema of the wheal that is raised with the drug or any systemic signs are an indication that the agent should not be used as a spinal anesthetic.

Clinical experience indicates that reactions suggestive of sensitivity are much more likely when the agents are repeatedly injected at intervals of several days and that the quantity used is of little importance whereas in most toxic reactions the quantity is likely to have been excessive. While preadministration of a barbiturate appears to forestall the pharmacologic untoward effects it seems to have little influence on the allergic type of manifestation.

B HORMONES

Hormones belong to the group of endogenous allergens. Although many hormones used therapeutically are of animal origin they can be considered as falling in this category provided the sensitivity is organ specific (e.g. insulin liver) and not species specific (i.e. to the muscle serum or protein of the animal species from which the extract is obtained). The principal points concerning hypersensitiveness to this type of allergen have been discussed on page 128. We shall here consider principally the symptomatology of these conditions. It must be stressed however that we shall refer only to observations in which allergy to the glandular secretion *per se* has been proved to exist excluding from consideration those cases in which the hypersensitiveness is in relation to the protein of the animal from whose glands the hormone has been derived or to the menstruum (e.g. peanut oil) in which the hormone is dissolved.

Insulin hypersensitiveness is by no means uncommon. Reports on the subject differ extraordinarily however since many authors include even the mildest local reactions while

others see fit to recognize only severe constitutional symptoms. Allan and Scherer¹²⁰ take more or less of a middle course, reporting a finding of hypersensitiveness, among 18,000 diabetics treated with insulin, amounting to 14 per cent. The symptoms are extremely varied: (1) mild local reactions at the sites of injections (e.g., local urticaria); (2) severe local reactions, such as swelling, infiltration, and even pseudoerysipelas to pseudo-phlegmonous swellings terminating in sterile abscesses, possibly the expression of an Arthus phenomenon (Lereboullet and his associates, Achard and Bloch), (3) general reactions—

in about 20 per cent of patients within 7 to 10 days after starting treatment, according to Goldner and Ricketts¹²¹. This may be accompanied by itching and induration. It usually does not interfere with the action of insulin and will disappear without special care in one or two weeks, or sometimes when the brand of insulin is changed, and particularly if the injections are given intramuscularly (see below). On the other hand, there is always a possibility that some of the local reactions may be nonspecific, due to preservatives or to incomplete elimination of the alcohol used for sterilizing the syringe and needle.



FIG 154. GENERALIZED URTICARIA APPEARING NINE DAYS AFTER START OF INSULIN TREATMENT

pruritus, generalized urticaria (FIGS 154, 155), morbilliform and scarlatiniform erythemas, dermatitides, angioneurotic edema, including edema of the glottis, as well as asthma, nausea, vomiting, abdominal cramps, painful swelling of the joints (Johnson¹²²), purpura (Kern and Langner¹²³), fever, and anaphylactic shock. The resemblance of some of the insulin reactions to serum sickness has been pointed out by many authors.

Swelling and erythema at the injection site persisting for one-half to several hours appear

Another local complication is insulin atrophy or insulin hypodystrophy—a benign, essentially noninflammatory lesion restricted to simple disappearance of adipose tissue at the site of injection (FIG 156). The condition is limited almost exclusively to persons under the age of 20 or to adult females. It is not rare—Beckert¹²⁴ observed 37 cases in a series of 169 diabetics treated more than four years. No definite cause has been ascertained. Some observers have implicated the acid pH of the insulin employed, some undetermined in-

¹²⁰ ALLAN, F. N., and SCHERER, L. R. *Endocrinology* 15: 417, 1932

¹²² JOHNSON, A. S. *New England J. Med.* 311: 321, 1934

¹²³ KERN, R. A., and LANGNER, P. H. *J. A. M. A.* 113: 198, 1939

¹²¹ GOLDNER, M. G., and RICKETTS, H. T. *J. Clin. Endocrinol.* 2: 293, 1942

¹²⁴ BECKERT, W. *München med. Wochenschr.* 88: 336, 1941, abstr. *J. A. M. A.* 117: 17-1, 1941

trinsic factor in certain patients local traumatism and simple local lipolysis in individuals who are peculiarly susceptible. A few authorities have suggested that lipolysis

determine whether the patient is allergic to the various forms of insulin and to choose one to which he does not react. Local traumatism should be diminished by using the higher con-

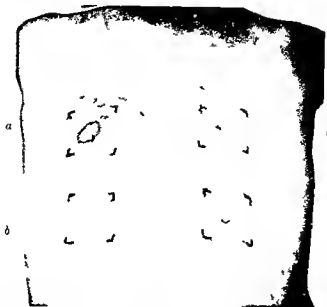


FIG 155 PASSIVE TRANSFER OF HYPERSENSITIVENESS TO CRYSTALLINE INSULIN WITH
FRAUSNITZ KUESTNER TECHNIC

a = react on bet ween serum of patient shown in FIG 154 and insulin b c d = negative results with various controls

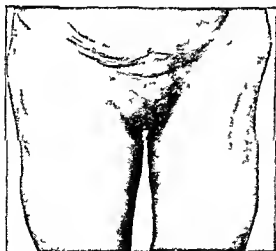


FIG 156 INSULIN LIPODYSTROPHY
Local fat atrophy due to insulin

trophy might be due to a bizarre form of allergy and Joslin has recommended that insulin from different animal sources should be tried. It is helpful to perform skin tests to

centrations of insulin thereby reducing the bulk of each injection by spacing successive injections widely and by avoiding the use of chemical solutions particularly bathing or rubbing alcohols in sterilizing the syringe and needle.

It appears that generalized insulin allergy occurs chiefly in middle aged or older patients with moderately severe diabetes. Interruption of treatment with insulin predisposes to allergy. Therefore cutaneous tests are advised in patients in whom treatment is resumed after a lapse. Experimental confirmation of allergization to insulin itself was offered by Wasserman and Mirsky¹⁴ since animals sensitized to beef insulin were shocked by pork sheep and bison insulin and parallel complement fixation reactions were obtained.

As regards the modified insulins Page and Bauman¹⁵ showed that cutaneous reactions

¹⁴ WASSERMAN P. and MIRSKY I. A. Endocrinology 31: 15, 1942

¹⁵ PAGE R. L. and BAUMANN L. J. A. M. A. 124: 704, 1944

to protamine are more frequent than to globin in allergic and non-allergic patients, and to beef insulin more than to crystalline insulin. Diabetic patients receiving injections of protamine zinc insulin appear to become desensitized to protamine, while those to whom globin insulin with zinc had been administered daily for years were not sensitized to globin.

Local reactions can often be avoided by performing the injection with a needle other than the one used for drawing up the insulin, in order to avoid contact between the allergized skin and the traces of insulin on the outside of the needle. If this is not successful, the injection should be given intramuscularly (with a long needle) rather than subcutaneously. Finally, in order to guard against hypersensitiveness to the protein of the animal from which the insulin was derived, it is advisable to change to a brand of insulin prepared from another animal species, or better, to crystalline insulin. This precaution is recommended because skin tests with animal protein are often "false negative."

None of these measures will be effective in the treatment of a generalized allergy to insulin per se. Three specific methods are available for dealing with a true insulin hypersensitiveness. (1) Hyposensitization may be tried, beginning with 1 unit of crystalline insulin diluted in 1 cc. of saline, injected subcutaneously. The dose is to be increased by 1 unit daily, if possible. In this manner, the desired effect can be achieved within one to four weeks. The degree of hypersensitiveness may be so high in some cases that treatment must be initiated with as little as 0.00001 unit. The greatest caution must be exercised at all times, for occasionally patients are so incredibly hypersensitive that severe general manifestations are not unlikely. There are two main disadvantages of this method: the long time required, and the fact that it cannot be used in the case of a patient whose daily insulin requirements are high. (2) Some authors (Umber and Stoetter) have reported success, in cases that were not too severe, with the skeptophylactic deallergization method. A dose of $\frac{1}{2}$ to 1 unit is injected subcutaneously forty-five minutes before the main injection. (3) Bayer¹²¹³ and Corcoran⁵⁰³ recommended

the rapid or "rush" desensitization method—or, as we prefer to call it, the rapid deallergization method (p. 214). This procedure is to be employed only by experienced physicians and only on hospitalized patients, since manifestations of shock often appear. With these precautions, the results are highly satisfactory in the writers' experience. In Weitz's case¹²¹⁹ desensitization with crystalline insulin required 5 days, and resulted in a reversal of direct skin and passive transfer tests to negative.

Finally, there are also some nonspecific measures worthy of mention, such as subcutaneous injection of gradually increasing doses of histamine (Collens and his associates⁵²) three times weekly, or of histamine-azoprotein every three days (Hughes and McAllister¹²²⁰).

A comprehensive review of the important problem of insulin allergy has been contributed by Harten and Walzer.²⁴⁹

The frequency with which insulin resistance is associated with insulin allergy was revealed in the cases collected from the literature by Martin et al.²⁶⁴ and has attracted considerable attention,¹²²¹ although the relationship is not constant. Other factors, such as acidosis, infections, sepsis, endocrine disturbances, liver disease, and the so-called insulin antagonist appear to play a part. To achieve clarity of terminology, Goldner and Ricketts¹²²⁴ recommend that the term allergic be used to refer to symptoms due to the antigenic property of insulin as a protein substance, and sensitivity or insensitivity (i.e., insulin resistance) to refer to the body's response to the specific metabolic function of insulin as a hormone. On the basis of his clinical observations and the demonstration of specific precipitins in patients with insulin resistance during infections, Root²⁶⁹ has suggested the hypothesis that, in the presence of diabetes, an infection may stimulate the antigenic mechanism in such a way as to produce antibodies not merely to the specific invading organism but to insulin as well—an example of parallergy. The sera of 6 insulin-resistant cases reported by Lerman²⁶⁹ gave positive precipitin and

¹²¹⁹ WEITZ, M. A. *J. Allergy* 14: 229, 1943.

¹²²⁰ HUGHES, R. F., and McALLISTER, H. R. *Ann. Allergy* 3: 207, 1945.

¹²²¹ Editorial. *J. A. M. A.* 121: 52, 1943.

¹²¹³ BAYER, L. M.: *ibid.* 102: 1934, 1934.

Prausnitz Kuestner passive transfer reactions in 2 and passive transfer only in 2 others. Although quantitative differences occurred the reactions were essentially alike with insulins from all animal sources indicating hormone specificity rather than species specificity. Patients recovering from insulin resistance usually turn out to be severe diabetics. In Lowell's case²⁰ desensitization resulted in a transitory response although the insulin resistance returned despite continued administration of insulin and both allergy and irresponsiveness recurred after insulin was withheld. Interestingly human insulin caused a greater drop in blood sugar than did the commercial crystalline product. His findings on injecting patients' serums into animals seemed to indicate the presence of two types of antibodies: an allergic antibody and an insulin neutralizing antibody. In this connection it may be noted that the animal experiments of Wasserman and Mirsky¹²⁴ showed that the antigenic property of an insulin preparation had no relationship to its physiologic activity.

Allergic reactions to *pituitary extract* prepared from the posterior lobe of the pituitary gland seem to be rare. Through the year 1939 Harten and Walzer⁶⁹ found only 22 satisfactorily proved cases in the entire literature. The symptom most commonly observed is generalized urticaria; others are pruritus, angioneurotic edema, asthma, nausea, vomiting, and abdominal cramps. Forro and Lendvai reported successful hyposensitization in 1 case.

Only 1 case of hypersensitiveness to *antitoxin S* has been reported (Vaughan and Pipes¹³²). However, other patients who were sensitive to posterior pituitary extract gave positive cutaneous reactions to antitoxin S as well.

Hypersensitiveness to *liver* injections given for pernicious anemia and other conditions is comparatively rare. However, despite progressive refinements in the manufacture of liver extracts, several reports of proved allergic reactions have appeared in the last few years (Andrews¹²⁵, Taylor and Hilger¹²⁶, Fein-

berg, Alt, and Young¹²⁴, Scarlett and Macnab¹²⁵⁷). Rynes and Tocantins¹²⁵⁸ tabulated at least 48 cases from the literature and Kaufman, Farmer, and Reich¹²⁵⁹ 50 cases to which they added one and eleven more respectively. However, there must be many more reactions than the published reports indicate, the commonest type being urticaria. Thus the writers have quite often been forced to discontinue parenteral liver therapy on account of local and also general allergic manifestations. Murphy¹²⁶⁰ encountered two severe reactions in the course of 1000 injections. But the total incidence must be considered as very low in view of the widespread use of liver therapy. In most cases the acquired sensitivity is one to an organ and not to a biologic source; in other words, the patients are hypersensitive to liver extracts derived from all animal species tried. Skin tests by Feinberg et al¹²⁵⁶ indicated that the antigen is associated with the anti-anemic factor but not identical with it, since sensitive patients did not react to tests with special extracts made from human liver. It is noteworthy that liver-sensitive patients tolerate liver by mouth as well as injections of extracts of muscle, serum, and other tissues of the same animals.

Reactions to liver usually occur in cases who have had a number of injections and most frequently after treatment has been discontinued and then resumed, or when the intervals between injections are unduly long (three weeks). Generally they are mild at first and tend to become progressively more severe as injections are continued. The brand of extract and the dosage have little relation to their occurrence.

In cases where there is a suspicion of hypersensitiveness, intracutaneous testing should be undertaken with extreme caution, since very severe immediate and delayed reactions have been reported. Crieep⁷⁵ described positive reactions to dilutions as high as 1:100,000 while all of Feinberg's¹²⁵⁶ cases reacted to dilu-

¹²⁴ LOWELL F. C. J. Clin. Invest. 23: 225, 233, 1944.

¹²⁵ VAUGHAN W. T. and PIPES D. M. Am. J. Digest. Dis. & Nut. 3: 558, 1936.

¹²⁶ ANDREWS C. T. Lancet 1: 664, 1941.

¹²⁷ TAYLOR C. B. and HILGER D. W. J. A. M. A. 117: 1880, 1941.

¹²⁵⁸ FEINBERG S. M., ALT H. L. and YOUNG R. H. Ann. Int. Med. 18: 311, 1943.

¹²⁵⁹ SCARLETT E. P. and MACNAB D. S. Canad. M. A. J. 46: 578, 1942.

¹²⁶⁰ RYNES S. E. and TOCANTINS L. M. J. Allergy 15: 173, 1944.

¹²⁶¹ KAUFMAN R. E., FARMER L. and REICH P. Ann. Int. Med. 19: 768, 1943.

¹²⁶² MURPHY W. P. Am. J. M. Sc. 186: 271, 1933.

tions ranging from 1:100 to 1:1,000,000. Obviously, therefore, it is dangerous to employ 0.1 cc. of the undiluted extract for intracutaneous testing, as generally recommended. Skin testing is not an absolute criterion since the intradermal test is difficult to interpret, although Kaufman, Farmer, and Reich¹²⁵⁹ feel that a wheal with pseudopods greater than 15 mm. in diameter is to be considered as a positive reaction when less than 0.05 cc of the material has been used.

Not all reactions appearing after injections of liver extract are to be interpreted as allergic. For despite all attempts at purification, most preparations contain a vasodilator substance that (particularly when administered intravenously) may produce acute histamine-like reactions characterized by a fall in blood pressure, nausea, and vomiting. These may occur at any time during the course of therapy and may not follow subsequent injections in the same patient. Local erythemas, pain, and tenderness not infrequently appearing at the injection site and sometimes associated with slight fever, not to mention local induration which may become secondarily infected and require surgical drainage, are not necessarily allergic in character. Such reactions usually cease to appear as therapy progresses, and are probably caused by irritative impurities in the preparations employed (Engelhardt and Derbes¹²⁶⁰). However, Rynes and Tocantins¹²⁵⁵ observed a patient with Arthus-like local reactions following the first and each subsequent injection of a commercial pork liver extract, specificity being proved by positive skin and passive transfer tests. Local allergic reactions are characterized by redness, heat, edema, and pain, and usually become progressively worse as injections are repeated. General allergic reactions comprise pruritus, urticaria, angioneurotic edema, asthma, dyspnea, tachycardia, vasomotor collapse, chills, fever, loss of consciousness, weakness, increased perspiration, and anaphylactic shock. They can be controlled by epinephrine, ephedrine, and calcium.

The therapeutic approach depends, of course, on whether the hypersensitiveness is

species-specific or organ-specific. In the former case, an extract consisting, for example, exclusively of pork liver (liver extract, Lilly) or of horse liver (Chappel's liver extract) can be used. In the latter case, hyposensitization may be attempted by means of graduated daily injections of liver extract (Andrews¹²⁵⁴). Feinberg¹²⁵⁶ found that hyposensitization often is only partial in degree, the patients failing to tolerate full therapeutic doses; other authors report varying success. Oral administration of liver extracts, as demonstrated by Criepe,⁷³³ often brings about a state of tolerance to the injections. We should like to term this last method "oral deallergization."

In the case of Rynes and Tocantins,¹²⁵⁵ subcutaneous hyposensitization was successful but the persisting inadequate hemopoietic response of the pernicious anemia was thought to be due to an allergic reaction of the blood-forming organs. This is analogous to the comparable situation of insulin resistance in cases of insulin allergy.

Allergy to *pancreatic tissue* has been reported in 2 cases by Criepe⁸⁴³. The reactions simulate those of serum sickness. Rowe⁷⁴⁰ has observed, in a few patients, migraine and gastro-intestinal symptoms following oral administration of powdered pancreatin and trypsin.

Despite the extensive use of *estrogenic substances*, only very few reports of hypersensitiveness to these can be found in the literature. Thus, Harten and Walzer⁵⁴⁹ mention 2 cases reported by Burnberg and Golan: local urticarial swelling followed injections of amniotin, and subsequent oral administration of progynon DH not only brought on a flare-up of these manifestations, but was followed a week later by generalized urticaria and angioneurotic edema. Loftis¹²⁶² reported the case of a patient with purpuric lesions caused by estrogenic substances. Our consideration here excludes those cases, however, in which the hypersensitiveness was in reaction to the oil used as a vehicle. Levison and Harrison¹²⁶³ observed such a case, in which the hypersensitiveness was related to cottonseed oil and peanut oil.

¹²⁵⁹ LOFTIS, E. L. Arch. Dermat. & Syph. 42: 138, 1940.

¹²⁶³ LEVISON, L. A., and HARRISON, J. J. J. A. M. A. 113: 2055, 1939.

¹²⁶⁰ ENGELHARDT, H. T., and DERBES, V. J. Southern M. J. 37: 31, 1944.

Zondek and Bromberg⁵³⁶ have shown that properly performed intracutaneous tests with crystalline steroid hormones including the estrogenic and androgenic substances may be used to confirm hypersensitivity to these endogenous allergens (p. 131).

Two cases of severe generalized acute urticaria following intramuscular injections of testosterone were reported by Mitchell.⁶⁴

The one known case of allergy to the active principle of thyroid extract was described by Vaughan.²¹



FIG. 157. NECROSIS AND SCARRING IN ASTHMATIC PATIENT DUE TO ADRENALIN

It cannot as yet be definitely affirmed that there is such a thing as allergy to epinephrine. The only convincing case on record is that of Dumm.⁵⁵⁴ The senior author* (FIG. 157) Cohen and Waterstone⁶⁶ and others have described cases of extensive sloughing of tissues following injections of epinephrine. The question arises however as to whether the tissue injury is due to (1) an allergic hypersensitivity (2) the vasoconstrictive action of the drug and the resulting prolonged is

chemia of the tissues (3) the toxicity of epinephrine per se or (4) the irritating effect of a preservative. We believe that in the case we observed (and the same may very well be true of the cases reported by others) the cause is to be found in the traumatic damage together with the vasospastic effect of the epinephrine rather than in an allergic hypersensitivity to the drug.

C. VITAMINS

As was to be expected the great increase in the use of vitamins has brought on a number of cases of hypersensitivity to them. Strangely enough however the only reports so far made refer to thiamin hydrochloride. Reingold and Webb⁵⁵⁶ reported a death occurring within ten minutes after the patient received her fourth intravenous injection of 100 mg. The cases described by Stiles,⁵⁵⁷ Schiff,⁵⁵⁸ and Laws⁵⁵⁹ began with rhinorrhea and local urticaria followed by severe collapse while that of Stein and Morgenstern⁷⁹ had generalized pruritus asthma cyanosis shock and loss of consciousness for 24 hours after the eighth subcutaneous injection and that of Leitner⁵⁵⁷ asthmatic attacks and pronounced eosinophilia after the fourth. In some of them passive transfer was strongly positive. Stiles pointed out that skin tests are to be made with weak dilutions (0.03 cc. of a preparation containing only 5 mg. per cubic centimeter) since stronger concentrations are nonspecifically irritating. Kalz⁵⁷² found that thiamin hydrochloride was an obligate urticarogen agent probably by inhibiting acetylcholinase the enzyme which destroys the acetylcholine set free at the end organ.

During a course of treatment with betaxin injections the senior author observed marked local swelling associated with pruritus following the sixteenth injection the seventeenth injection was followed by an immense red dened local reaction together with a marked

⁵⁵⁶ REINGOLD, J. M. and WEBB, F. R. J. A. M. A. 130: 491, 1946.

⁵⁵⁷ STILES, M. H. J. Allergy 12: 507, 1941.

⁵⁵⁸ SCHIFF, J. L. J. A. M. A. 117: 609, 1941.

⁵⁵⁹ LAWS, C. L. Ibid. 117: 176, 1941.

STEIN, W. and MORGENSTERN, M. Ann. Int. Med. 20: 826, 1944.

⁵⁷² LEITNER, Z. A. Lancet 2: 474, 1943.

⁵⁷ KALZ, F. J. In: C. G. Dermat. 135, 1942.

⁵⁴ MITCHELL, J. H. Lecture in the Club of Allergy, Sec. 8, 91, 1943.

⁵⁵ URBACH, E. Med. Klin. 32: 769, 1936.

COHEN, A. E. and WATERSTONE, M. L. J. Allergy 11: 393, 1940.

flaring up of all the old injection sites. A similar phenomenon was seen by Bowen¹²⁷² in a case with intense urticaria and angioneurotic edema following the eighth injection of thiamin.

Mitrani¹²⁷¹ reported successful subcutaneous hyposensitization of a patient with a maculopuriginous eruption of the face, chest, and back produced by a single injection of 50 mg. of thiamin hydrochloride. Eisenstadt's¹²⁷³ two cases with proved sensitivity to injections of the drug were able to tolerate it by mouth, possibly because by this route there may not have been a sufficiently high level at any one time to evoke an allergic reaction.

D. FOREIGN SERUMS

Parenteral administration of foreign serums occasionally brings on a number of symptoms collectively designated as "serum disease." These symptoms are of three principal types: (1) the delayed reaction, generally called "serum sickness," appearing about eight to twelve days after the first injection; (2) the accelerated reaction (or accelerated serum sickness) occurring after five days or even earlier, in cases in which the second injection is given after an interval of at least four months; (3) the immediate reaction, generally known as anaphylactic shock, occurring in cases in which the second injection is given after an interval of less than four months, and also in individuals who apparently have a "natural" hypersensitiveness to serum (see below).

Following local injection, a severe local reaction may appear within twenty-four to forty-eight hours, corresponding to the Arthus phenomenon in experimental animals.

Most authorities are now of the opinion that there is no fundamental difference between serum sickness and serum shock (anaphylactic shock): "Every single phase of the serum sickness problem has its counterpart in lower animal anaphylaxis" (Ratner).

1. SERUM SICKNESS

The clinical picture of serum sickness was described as early as 1667 by Denis, who had

undertaken transfusions with lamb's blood. But it was Johannsen (1895) who first advanced experimental proof of the fact that foreign blood can be the cause of disease. Credit is due most especially to von Pirquet and Shick,¹²⁷⁶ however, for their contributions toward a better understanding of the disease—both in identifying it as the expression of an allergic reaction and in giving it its name.

a) PATHOGENESIS

The fact that serum sickness is an allergic disease is based on the following observations. (1) The latent or "incubation" period (eight to twelve days) corresponds with the average time necessary for the formation of antibodies, and is shorter after reinjection than after the first injection. (2) The blood of persons who are suffering from or who have recovered from serum sickness contains antibodies—i.e., the serum of such individuals is capable of passively allergizing guinea pigs (De Besche) and of locally sensitizing the skin of normal individuals by means of the Prausnitz-Kuestner technic (De Besche, Ramel). (3) Precipitins can be demonstrated in the blood of both human beings and animals suffering from serum sickness (Marfan and Le Play; others).

In order to explain the occurrence of serum sickness following the primary injection of serum, von Pirquet and Shick¹²⁷⁶ advanced the following hypothesis, now almost universally accepted: the injection of foreign serum incites the production of antibodies, which generally takes eight to twelve days; when the antibodies have been formed, they enter into a reaction with the remaining portion of the antigen, resulting in exanthems or any of the symptoms that will be mentioned below. In other words, the foreign serum enters into the process in two ways: as the stimulus to antibody production, and as a component of the antigen-antibody reaction.

By the time of the second or third injection, the tissues are already allergized—i.e., they either contain specific antibodies or are capable of producing them more rapidly than before. This explains the immediate and accelerated reactions, and also, to a certain ex-

¹²⁷² BOWEN, R.: Letters, Internat. Corr. Club of Allergy, 1944.

¹²⁷¹ MITRANI, M. M.: J. Allergy 15: 1-9, 1944.

¹²⁷³ EISENSTADT, W. S.: Minnesota Med. 25: 351, 1942.

¹²⁷⁶ PIRQUET, C., VON, and SCHICK, B.: Die Serumkrankheit. Vienna: Deuticke, 1903.

tent the increased severity of the clinical response

It has occasionally been observed that a single injection is followed by two three and even as many as four separate and distinct attacks of serum sickness between which there are intervals sometimes as long as several days Doerr explained this on the basis of the fact that the formation of antibodies to the various proteins contained in the whole serum—such as euglobulin pseudoglobulin and albumin—does not take place simultaneously but rather in successive stages This assumption is supported by the fact that such relapses of serum sickness do not occur when only one of the proteins—e.g. pseudoglobulin—is injected Another view is that the various proteins contained in the serum do not always act at the same time or in other words that the reactions they enter into do not always coincide thus bringing on the symptoms of serum sickness at different times

In the great majority of all these cases allergization has been caused by previous parenteral administration of the foreign serum However—and this is of considerable importance with regard to the question of natural or innate serum hypersensitivity—allergization can also be produced in other ways Aurichio⁷⁷ reported 2 cases in which the patients following oral administration of a preparation containing horse serum acquired hypersensitivity of such degree that one of them later died of anaphylactic shock after an injection of therapeutic serum and the other reacted with severe local manifestations Observations similar to these were made by the senior writer⁷⁸ when a series of experiments with orally administered horse serum propeptan was carried out in an attempt to reduce the incidence of serum sickness It was found that the patient receiving this preparation reacted more promptly and with more severe serum exanthems than did controls—definitely indicating allergization Ratner¹⁷⁹ called attention to the observations of French investigators who reported a large percentage of severe serum reactions in patients who regularly ate

horse meat Kolle and Hetsch reported that Tartar children who were brought up on mare's milk or who were fed horse meat presented especially severe manifestations when given antitoxins containing horse serum

Moreover sensitization may also occur by means of inhalation Forster¹⁸³ and Ratner and Cruehl¹⁸⁴ have shown that there is an antigenic element common to horse dander and horse serum In principle it is possible therefore that an individual who through contact with horses has become sensitized via inhalation may also have acquired hypersensitivity to horse serum

Furthermore allergization can also take place through the placenta Thus Brusa demonstrated that if a mother received serum during pregnancy the first injection of the same serum in the infant will evoke an allergic reaction with a shorter than average incubation time Ratner¹⁸⁵ showed that all offspring born of mother guinea pigs that had been allergized with horse serum before pregnancy were sensitive at the time of birth and that thus passively transferred sensitiveness persisted for three months He¹⁸⁶ also demonstrated active sensitization litters born from one to three days after their mothers had been given horse serum and receiving their first injection at the age of 1 month exhibited a definite hypersensitivity

Finally it must be pointed out that many patients—including even intelligent ones—do not know whether or when they have received inoculations with animal serum This is partly due of course to the fact that the serum was administered so long ago—usually during childhood—that the patient has simply forgotten about it The patient's ignorance may also be excused in many instances because of the fact that he was not informed of the nature of the injection or that he was given the injection while he was unconscious (when injured for example) or under anesthesia

These various possibilities—i.e. of oral bronchial or placental sensitization as well as of parenteral sensitization without the patient's knowledge—have been discussed in some detail in order to show that one may

⁷⁷ AURICHIO L. *Pediatrics* 39: 289 1931

⁷⁸ URBACE E. *Wien med Wochenschr* 59: 1398 1937

¹⁷⁹ RATNER B. *discusses on* to Tuft

¹⁸³ Idem JACKSON H C and CRUEHL H L. *J Immunol* 44: 303 1927

never speak with assurance of "innate" hypersensitiveness to foreign serum

However, serum disease can be caused not only by foreign serum, as employed in the prophylaxis and therapy of infectious diseases, but also under certain circumstances by *homologous serum*, as used in autogenous or convalescent serum therapy (Netter; Marie; Nelli, Fox and Hardgrove¹²⁵¹, McKhann¹²⁵²; Heller, others). Bloxson¹²⁵³ has reported that five doses of 0.4 cc. of convalescent serum intradermally is quite effective in the prophylaxis of measles and gives rise to practically no untoward effects; 1 case in 40 treated had mild local urticarial reactions. In this way, the reactions sometimes seen after larger doses given subcutaneously may be avoided.

A case of severe anaphylactic shock with death has been described following the second dose of 2 cc. of immune globulin.¹²⁵⁴

Human plasma, now in wide use in the treatment of shock, burns, hemorrhage, and other conditions, is not without its reactions, some of them on an allergic basis. It is important to distinguish between those due to a single specimen of unpooled or monovalent plasma, and those due to plasma pooled from a number of donors under standard requirements. The pooling appears to inactivate, by mere dilution, such substances as antigens, haptens, and antibodies, and by suppression or adsorption of the agglutinins which may be present in individual samples. The percentage incidence of reactions to pooled plasma appears to be low, but they are far from unknown.

A near-fatal reaction to human plasma was reported by Polayes and Squillace,¹²⁵⁵ although the possibility that the reaction was due to a preceding infusion of dextrose in saline solution cannot be eliminated,¹²⁵⁶ and typical allergic shock by Levine and State.¹²⁵⁷

Müller and Tisdall¹²⁵⁸ have analyzed the types of reactions to pooled human plasma transfusions, and point out that in addition

to the allergic type, there are several others, including thermal or pyrogenic reactions, hemolytic reactions, toxic reactions due to anticoagulants or preservatives, transmission of infectious diseases from the donor, reactions due to bacterial contamination, pulmonary embolism, cardiac failure due to overloading of the circulation, and miscellaneous reactions, possibly on a psychic basis. Among 10,000 such transfusions, they observed 105 reactions of the allergic type, all urticarial in nature except three which were characterized by asthmatic breathing. Their experience convinced them that many are due to hypersensitiveness to a normal substance common to the plasma of many donors, although others are due to *allergens in the plasma and to passive transfer of sensitivity from donor to recipient*. More severe forms, including loss of sphincteric control and anaphylactic shock, have been seen by Kilduffe and DeBailey¹²⁵⁹ and others following transfusions. Strumia, McGraw, and Blake¹²⁶⁰ estimate the incidence of the allergic reactions to transfusions of whole blood, plasma, or serum at 0.3 to 1.0 per cent, they mention local or general urticaria, angioneurotic edema, fever, and occasionally asthma and edema of the glottis. According to Maunsell,¹²⁶¹ reconstituted dried serum gave positive intradermal skin tests in 77 per cent of allergic subjects, the degree varying with different human serums, and in 20 per cent of non-allergic subjects. Autoserum failed to produce reactions in any case. After transfusion, reactions ensued in 14 of 17 allergic patients, but in none of the non-allergic. Repeated injections gave rise to no evidence of sensitization, but desensitization occurred in 10 of 11 serum-sensitive allergic patients. It is of interest that in asthmatics the latter change of reactivity was accompanied by a marked improvement in the asthma. Maunsell states that nothing is known of the source or character of the antigenic substance in human serum, although the presence of extraneous ingested or inhaled allergens must be considered. It might

¹²⁵¹ FOX, M., and HARDGROVE, M. J. A. M. A. 168: 586, 1937.

¹²⁵² MCKHANN, C. F. *ibid* 169: 2031, 1937.

¹²⁵³ BLOXSON, A. J. *Pediat* 26, 32, 1935.

¹²⁵⁴ QUERIES and MINOR NOTES. J. A. M. A. 124: 472, 1944.

¹²⁵⁵ POLAYES, S. H., and SQUILLACE, J. A. *ibid* 118: 1030, 1942.

¹²⁵⁶ Editorial *ibid* 121: 916, 1943.

¹²⁵⁷ LEVINE, M., and STATE, D. *Science* 96: 68, 1942.

¹²⁵⁸ MÜLLER, E. B., and TISDALL, L. H. J. A. M. A. 128: 863, 1943.

¹²⁵⁹ KILDUFFE, R. A., and DEBAILEY, M. *The Blood Bank and the Technic and Therapeutics of Transfusions*. St. Louis: Mosby, 1942, p. 500.

¹²⁶⁰ STRUMIA, M. M., MCGRAW, J. J., JR., and BLAKE, A. *Ann Int. Med.* 19: 718, 1943.

¹²⁶¹ MACNELL, K. *Brit. M. J.* 2, 236, 1944.

be possible to prevent many of these untoward reactions by first performing an intracutaneous test with the plasma, if feasible

The fact that homologous serum can cause serum disease—even, though very rarely, fatal anaphylactic shock (Schmidt)—was ascertained in human experiments by Tezner and Reiter and Nathan and Grundmann, and in animal experiments by Eickhoff

We exclude from consideration here, of course, those cases in which allergic reactions follow transfusions clearly owing to the introduction of an excess of allergen in the blood of the donor. Thus, a patient allergic to milk will react to blood from a donor who has ingested milk shortly before giving the blood. A pertinent case was reported by Dickstein,¹²⁹⁷ the severe urticaria was shown to be due not to the pooled human plasma per se, but to its demonstrable content of such antigens as milk, beef, and lamb, the patient being detectably sensitive to these foods. Conversely, passive introduction of an antibody into a recipient who has the corresponding antigen in his blood, will also produce allergic reactions. The latter situation is illustrated by a case reported by Berger¹²⁹⁸ to arrest hemorrhage, the patient received horse serum, and some days later a blood transfusion from a donor who was a horse asthmatic. Colonnell¹²⁹⁹ observed a patient in whom both mechanisms were operative: he was passively sensitized by transfusions from a donor with ragweed pollen allergy, urticaria, angioneurotic edema, asthma, and laryngeal edema with dysphonia and dysphagia followed intravenous administration of pooled plasma which was shown to contain ragweed pollen allergen. All authorities are agreed that plasma donors should be in a fasting condition and that the pools should be prepared from as many samples as possible, it has also been suggested that prospective donors with active allergic states or receiving any form of injection therapy should be rejected.

Reactions to intravenous infusions of Rh positive blood in isosensitized individuals will be considered in the next section

Mention must also be made here of the cases of serum sickness following trauma resulting in hematomas of the subcutaneous tissues or joints, or following operations leading to serous effusions. The fact that homologous serum can acquire the character of an antigen is perhaps best explained by the concept that the blood serum or tissue fluid becomes foreign to the organism, owing to chemical alterations induced by the trauma—or, in other words, an endogenous allergen is formed (see p. 122).

Voss^{1300, 1301} has contributed very interesting and important studies on the production and prevention of serum exanthems, by means of human convalescent serum, in individuals recently treated with animal serum. He showed that when a child that has received diphtheria antitoxin, for example, is given an intravenous injection of 1 cc of convalescent serum on the following day, a palm-sized urticarial swelling will appear within three minutes at the site of the horse serum injection, and that, as a result, the child within a few days will be hyposensitized to such an extent that there will be no reaction even to an intracutaneous test with horse serum. If, however, 5 cc of the convalescent serum is injected intravenously four days after the treatment with diphtheria antitoxin, a universal serum exanthem appears. If the injection is given at the start of the spontaneous serum exanthem, the condition runs a very rapid course, with shocklike manifestations. Finally, if the injection of the convalescent serum is given when the spontaneous exanthem has almost faded, three additional attacks will appear, at intervals of two days. Voss assumes that the injection of convalescent serum increases the antibody titer to the concentration necessary for the production of serum sickness in an individual prepared with foreign serum.

This procedure also has a certain amount of therapeutic significance, for if the antiserum is injected promptly enough, one might be able to confine the antigen-antibody reaction to the site of the antitoxin injection.

This experimental procedure—called in verse or reverse anaphylaxis (Voss) and pas-

¹²⁹⁷ DICKSTEIN B. *Ann. Allergy* 2: 327, 1944.

¹²⁹⁸ BERGER H. C. *M. Clin. North America* 7: 1169, 1921.

¹²⁹⁹ COLONNELL W. J. *U. S. Nav. M. Bull.* 41: 1356, 1943.

¹³⁰⁰ VOSS E. A. *Ztschr. f. Kinderh.* 59: 612, 1938. *Klin. Wchnschr.* 17: 710, 1938.

sively acquired or merely passive serum sickness (Karelitz)—has been confirmed, by and large, by Szirmai,³⁹⁰ Karelitz and Glorig,³⁹³ and Karelitz.¹²⁹⁶ The last-named failed to corroborate all the therapeutic effects claimed for this method, although he did note that an episode of passive serum sickness altered the subsequent course of actively acquired serum sickness in horse serum treated children. The production of passive serum sickness does not appear to depend on the presence of precipi-

b) SYMPTOMATOLOGY

Serum sickness is characterized by cutaneous or subcutaneous manifestations, adenopathy, swelling of the joints, and fever. The initial symptom of the disease is generally enlargement of the regional glands. This is followed by fever, severe pruritus, and usually urticarial swelling and redness (Fig. 158) at the site of the serum injection; under certain circumstances, the latter may develop into a



FIG. 158. LOCALIZED SERUM EXANTHEM AT SITE OF INJECTION OF ANTITETANUS SERUM

tins in the serum, and the causative antibody was found in serums from horse serum treated patients who had failed to develop serum sickness. The presence of transferable antibodies was also demonstrated in the serum of patients convalescing from serum sickness by the Prausnitz-Kuestner and the reverse techniques. The method of passive serum sickness promises to be useful for the further study of the problems of the pathogenesis and prophylaxis of this disease.

hard inflammatory necrotic lesion (i.e., Arthus phenomenon). A few days later, but occasionally as the first symptom, an urticarial exanthem appears (Fig. 159); less frequently, an erythematous, morbilliform, or scarlatiniform eruption (Fig. 160), and, very rarely, hemorrhagic or exudative rashes that cover large parts of the skin and are accompanied by distressing pruritus. Very frequently not only the skin but also the subcutaneous tissues are involved, presenting various degrees of edema, particularly of the face (eyelids and lips). At the same time, there are swelling, redness,

¹²⁹⁶ KARELITZ S. J. *Mr. Sinatillop* 9, 921, 1943

pain and stiffness in the joints usually the large joints and generalized lymphadenopathy with considerable tenderness. The arthropathy may be confined to the temporomandibular joint (Turner and Clarke²⁹⁷) giving rise to rigidity of the jaw which must not be mistaken for a symptom of tetanus since consequent administration of more tetanus

tetanus and from his own observations and Schipkowensky²⁹⁸ has listed 80 cases that following repeated injections of serum presented paralysis in the areas of the muscles into which the injections were made (deltoid serratus anterior etc). These symptoms were tentatively attributed to urticarial lesions in the intervertebral foramina. Carmichael²⁹⁹ has reviewed the incidence of neurological sequelae following serum (and vaccine) therapy and pointed out that commissions to study this problem in England and the Netherlands disclosed well over 200 cases in 2 periods of 6 years. This category also in

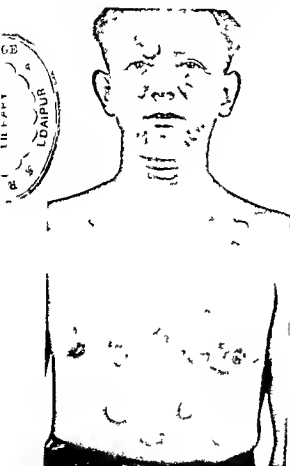


FIG 159 SERUM EXANTHEM TEN DAYS AFTER PROPHYLACTIC INJECTION OF TETANUS ANTITOXIN

antitoxin may be followed by a possible fatality. The spleen is often enlarged. The fever does not persist very long—at the most two to three days—but occasionally has a septic character.

Aside from the muscular pains, severe cases also present neurologic complications. Thus Doyle²⁹⁸ has compiled 49 cases from the litera-



FIG 160 GENERALIZED SERUM EXANTHEM AFTER INJECTION OF DIPHTHERIA ANTITOXIN

cludes isolated instances of optic neuritis, inner ear deafness, Meniere's syndrome, laryngeal nerve paralysis, and even meningeal disturbances. Weissenbach and Dreyfuss assumed that the cause was a localized edema in the nerve roots or in the nerve tissue itself. Wulff reported a case in which myelitis followed serum sickness and considered the possibility of a pathogenetic relationship between them. The headaches that so frequently accompany the disease are probably due to cerebral edema. In addition to the anaphylactic reactions, an alternative theory involves the activation of a latent virus always present in the body but dormant and innocuous under normal conditions and be-

coming pathologic or noxious only in response to some excitant which causes a biochemical change in certain tissues vulnerable to attack. Allen divides the neurologic complications into four groups: the radicular, neuritic, polyneuritic, and central nervous types. Even psychoses may occur. In some cases neurologic symptoms are the only manifestations of serum sickness. These symptoms may persist for periods of from six months to two years and may be seriously disabling. They usually disappear completely. However, Bennet reported that 20 per cent of those affected may be left with a residual weakness. (For further details, see chap. XXVI).

In occasional cases, asthma, gastro-intestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea, which may even be bloody), albuminuria, and hematuria are observed.

Especially severe cases manifest a fall in blood pressure and leucopenia. In the acute stage, the flocculation test for syphilis may be positive—a finding that, without associated evidence, should not be considered a proof of lues.

It must be noted that any one of the aforementioned symptoms—including the most constant ones, such as exanthems and fever—may be absent in a given case of serum sickness.

In the majority of cases, the symptoms of serum sickness follow the primary injection of foreign serum after an incubation period of from eight to twelve days. The longest incubation period reported is thirty-six days (Hildebrandt¹³⁰¹). According to Bullowa, the duration of serum sickness is from one to three days in 54 per cent of all cases, from four to seven days in 35 per cent, and longer in 11 per cent. Following the second injection, the symptoms usually arise between the second and the sixth day; occasionally, however, they appear immediately or after a few hours. In some instances the allergic manifestations do not occur until after a series of injections. The development of the accelerated type of serum sickness is less likely when reinjections are given from six to nine months or more after the primary injection.

According to Tonietti's findings, a popular

reaction on intracutaneous testing appears, on an average, in from six to seven days after the primary injection.

Serum sickness itself is a self-limited disease, but it not infrequently leaves the organism allergized and thus provides the foundation for other severe allergic conditions.

Rich's experiments regarding the relationship of serum sickness to periarteritis nodosa will be considered in chapter XXIX.

(c) INCIDENCE

The ever increasing employment of sulfonamides and penicillin in the treatment of infectious diseases, and of toxoids and vaccines in their prevention, has enormously reduced the frequency and importance of serum therapy and consequently of serum disease.

Regarding the incidence of serum sickness, it is necessary to differentiate between primary serum hypersensitiveness (reaction to the first injection) and secondary (reaction to reinjections). Lucchesi and Bowman,¹³⁰² Toomey and Kimball,¹³⁰³ Fox,¹³⁰⁴ and Ustvedt estimated the incidence of primary serum hypersensitiveness to comprise about 35 to 43 per cent of all cases. In respect to cases following reinjection, however, it rises to 60 per cent according to Meaver, and to 77.5 per cent according to Ustvedt, while Kojis¹³⁰⁵ found that secondary injection of diphtheria antitoxin increased the incidence of serum sickness by 50 per cent and that the anaphylaxis rate was 23 times greater than after primary injections. Furthermore, primary serum hypersensitiveness is much more likely to occur when the serum is administered intravenously. According to Iwerson, the figures are: 54 per cent of cases following primary injection, and 74 per cent of cases following reinjection.

The incidence of serum sickness depends upon many factors. The most important is the degree of purification, concentration, and despeciation of the antitoxic serums. The next in order of importance is the quantity of serum administered, for it has been shown that with the use of 100 cc, serum sickness will

¹³⁰¹ LUCCHESI, P. F., and BOWMAN, J. E. *J. A. M. A.* 103:1049, 1934.

¹³⁰² TOOMEY, J. A., and KIMBALL, E. R., JR. *J. Pediat.* 13, 258, 1939.

¹³⁰³ FOX, M. J. *J. Infect. Dis.* 61:341, 1937.

¹³⁰⁴ KOJIS, F. G. *Am. J. Dis. Child.* 64:91, 313, 1942.

¹³⁰⁵ HILDEBRANDT, A. *Klin. Wchnschr.* 14, 1563, 1935.

result in 90 per cent of all patients. Another significant consideration according to Hooker is whether the primary injection is made with a toxin antitoxin mixture or with some other therapeutic serum. Thus Gordon and Creswell¹³⁰⁶ report that, of 556 patients who had received toxin antitoxin, 74 per cent presented reactions to serum, while symptoms occurred in only 43 per cent of 151 individuals who had previously received only a therapeutic serum without toxin. Moreover, stronger manifestations are evoked by fresh serum than by serum that has been stored for some time. Appreciable differences are also observed in the action of serums from various species of animals. Hog serum is said to cause serum sickness as often as horse serum. Avian serum is reported not to produce serum sickness. Finally, the climate, the season, and above all the predisposition and the general condition of the patient, are important. According to Coca, the American Indian and the Negro seem to be less susceptible to serum sickness than are members of the white race. Age and sex, however, appear to have no bearing on the incidence of serum sickness.

Especially important is the statement of Tuft¹³⁰⁷ that allergic individuals are no more likely to have serum sickness than are the nonallergic. He is of the opinion, therefore, that the physician need not hesitate to give serum to an allergic patient—with the exception of course, of patients hypersensitive to horse dander. The latter precaution is not entirely axiomatic either, for, according to Tuft, serum will be tolerated by horse asthmatics who fail to react to skin and conjunctival tests.

2. SERUM SHOCK

In contradistinction to the more or less common syndrome that typically develops after an incubation period of several days (i.e., serum sickness) there are several types of immediate reactions, of which some appear to be based on immunologic mechanisms. The most important—because the most dangerous—is the shocklike type, which corresponds in every respect with experimental anaphylactic shock. It can appear from several seconds to

thirty minutes after the injection. Cooke has suggested that a reaction be considered anaphylaxis if it occurs within an hour or less after the administration of the allergen. The symptoms are urticaria, angioneurotic edema, lacrimation, itching of the nose and throat, mucoid nasal discharge, a harsh cough, dyspnea, marked apprehension and profuse sweating. There may also be nausea, vomiting and general prostration. Serum shock may terminate fatally within minutes or hours or the patient may recover completely. It is more likely to occur in patients with strongly positive cutaneous and ophthalmic reactions to serum, and after intravenous than after intramuscular or subcutaneous injection. The administration of an injection during serum sickness is particularly hazardous. (For a more detailed discussion, see chap. XX.)

Sometimes delayed reactions occur in from six hours to five days. The same symptoms are observed as in serum shock, but they are far less severe. Since serum sickness following reinjection of serum may be accelerated to such an extent that it appears on the second and even on the first day after the administration of serum, considerable difficulty has arisen at times in differentiating between a delayed serum reaction and accelerated serum sickness.

According to Harten and Walzer,¹³⁰⁸ the syndrome of serum shock, which is properly to be interpreted as an expression of anaphylactic shock, should not be confused with certain immediate reactions that are non-specific in character. These are said to be caused by a vascular reflex resulting from the slight trauma occasioned by the intravenous injection (Bullowa¹³⁰⁹) or from disturbances in the colloidal balance. Generally included here are the manifestations of collapse observed, according to Lord and Heffron¹³¹⁰ in 7 per cent of all pneumonia patients receiving intravenous serum therapy. This reaction is initiated by flushing of the face, dyspnea, cyanosis, lumbar or abdominal pain, rapid weak pulse, and apprehensiveness. It is usually

¹³⁰⁶ GORDON M. and CRESWELL S. M. *J. Prev. Med.* 3: 21, 1929.

¹³⁰⁷ TUFT L. *J. Allergy* 6: 25, 1934.

¹³⁰⁸ HARTEN M. and WALZER M. *ibid.* 11: 68, 1937.

¹³⁰⁹ BULLOWA J. G. M. *The Management of the Pneumonia*. New York: Oxford, 1937.

¹³¹⁰ LORD F. T. and HEFFRON R. *Pneumonia and Serum Therapy*. New York: Commonwealth Fund, 1938.

transient. For its control, Bullowa recommends artificial respiration, hot blankets, and routine shock treatment. Other manifestations belonging to this category are the thermal or febrile reactions, characterized by chill, elevated temperature, delirium, rigor, and malaise. These symptoms usually appear from forty-five to ninety minutes after intravenous injection of serum, but may occur earlier or even during the injection. Bullowa reported thermal reactions in 18 per cent of 755 cases, with three fatalities. He recommends inhalation of amyl nitrite for management of them.

3. LOCAL SERUM REACTION

Repeated local injections of serum very rarely bring on a disease picture that corresponds fully to the experimental Arthus phenomenon and that can thus be interpreted as local anaphylaxis. In the rare instances of this, the reaction has been observed to appear within forty-eight hours, in the form of severe inflammatory local swelling, with induration and tenderness. The injected skin site becomes hemorrhagic during the next few days, and this is followed by an extensive necrosis and sloughing. Death may occasionally result from sepsis following the local gangrene. (For further details, see p. 88).

4. DIAGNOSIS OF SERUM HYPERSENSITIVENESS

In every case in which foreign serum is administered either prophylactically or therapeutically, the possibility of an allergy to serum must be considered, and, in the event of an existing hypersensitiveness, its relative degree must be determined. Three methods are available: the history, the skin test, and the ophthalmic test. Unfortunately, the history is often unreliable, either because the immune serum was administered during the patient's childhood or possibly at a time when the patient was unconscious (e.g., under an anesthetic), or simply because the patient was not properly informed of the nature of the injection he was receiving; furthermore, it must be remembered that even intelligent patients often forget that they have received any such injection, particularly when there were no disagreeable consequences. Altogether, the significance of a negative history should never

be overrated. In an attempt to combat this obstacle, the senior author¹³¹ in 1936 suggested the general use of so-called tattoo markings. For this purpose, with every ampule of immune horse serum there would be packaged a bit of cinnabar dust, for example, and a special needle, every vial of beef serum would be accompanied by some black India ink, and so on. The physician would be obligated to make an appropriate tattoo each time he injected serum—recording the first injection by tattooing one dot, the second by two dots, etc., on a designated site, such as the lateral aspect of the patient's thigh. In this manner, any physician who might be called upon to treat the patient subsequently would immediately know the nature and the number of serum injections previously administered. This would certainly eliminate a great part of the risk now incurred in treating unconscious or shocked victims of accidents or war. Fornet, Vickers, and others have advocated similar systems of tattoo markings.

Skin tests should be given to all patients known to have received serum treatment. Since intracutaneous injection of even minute amounts of serum can bring on the most alarming constitutional reactions, use of the scratch technic is recommended (Rudolph and Cohen¹³²), with a 1:10 dilution of normal horse serum, to be followed, in the event of a negative result, by an intracutaneous test. The recommended dosage is 0.01 cc. of a 1:10 dilution of normal horse serum if the patient is nonallergic, a 1:100 dilution, if he is allergic; or a 1:1,000 or greater dilution if there is a known sensitiveness to horse dander or to horse serum. If negative results are obtained with high dilutions, subsequent tests should be made after twenty minutes with more concentrated serums, and finally with undiluted normal horse serum. For testing purposes, it is not advisable to employ the same immune serum that is to be given the patient later; for, as Foshay¹³³ has shown, specific immune serum produces an immediate erythematous and edematous reaction (sometimes called the "E-E phenomenon") that may readily be confused with the reaction of

¹³¹ URBACH, E. *Klin. Wchnschr.* 13: 1012, 1936.

¹³² RUDOLPH, J. A., and COHEN, M. B. *J. A. M. A.* 102: 900, 1934.

¹³³ FOSHAY, L. *J. Allergy* 6: 360, 1935.

serum sensitization. While Tuft is of the opinion that a negative skin test definitely rules out the existence of serum sensitivity, Davis¹³¹⁴ concluded, on the basis of extensive material, that the cutaneous test has little real value as an index of the degree of sensitivity, regardless of whether the outcome of the test is negative or positive. Kojis¹³¹⁵ however, found that in patients with positive intradermal tests, the incidence of serum sickness following inoculation with diphtheria antitoxin was 4 times, of anaphylaxis 35 times, and of mortality 11 times greater than when the reaction was negative. Waldbott¹³¹⁵ reported fatal anaphylactic shock in 2 cases in which preliminary skin tests failed to evoke a reaction.

Many authors prefer the ophthalmic test. The procedure is as follows. Provided there is no evidence of inflammation of the conjunctivae, a drop of horse serum (diluted 1:10) is placed in the lower conjunctival sac. A positive reaction is indicated by itching, burning, redness, and lacrimation within ten to thirty minutes. The reaction can be controlled by instillation of a drop or two of epinephrine solution (1:1,000). The eye test is generally considered to be more dependable than the intradermal test, especially for indicating those individuals who might exhibit severe reactions. On the other hand, there have been a few reports of death due to anaphylactic shock following the administration of horse serum in cases in which conjunctival tests for sensitivity had been negative. Furthermore, this method is of no value in the case of young children if they begin to cry during the test, for the tears naturally wash the serum out of the eye. According to Kojis,¹³¹⁵ if the conjunctival test is positive the incidence of serum sickness is 5 times and of anaphylaxis 173 times greater than if negative.

In short, it is best to begin with a scratch test, then, if this is negative, to perform the ophthalmic test, and to resort to the intradermal test only if the others have failed to elicit reactions. A syringe containing epinephrine solution should always be at hand, even when eye tests are being made, for these too, according to Brown and Sechizer, occasionally

cause constitutional reactions. It should be emphasized that patients receiving repeated injections should be tested each time the serum is administered, unless it is given daily.

Finally, when the history indicates that even the scratch method might be too dangerous in a given case, an indirect test may be made (passive transfer with the patient's serum to the skin of a recipient). Obviously, however, the element of time permits this technic to be used only infrequently.

On the basis of animal experiments and clinical analysis, Swineford¹³¹⁷ suggests the theory that when cutaneous, conjunctival, and intravenous tests for rabbit serum sensitivity are negative, anaphylactic reactions following injections of antipneumococcal rabbit serum are due to the phenomenon of reversed passive anaphylaxis in which the antigen is supplied by the infecting organism *in vivo*, and the anaphylactic antibody is provided by the injected antiserum. He tentatively proposes that cutaneous, conjunctival, and intravenous tests for sensitivity be performed with the immune serum, instead of or along with normal serum. Although a positive erythema edema reaction (Toshay) may be anticipated on skin testing, this would indicate the presence of the pneumococcal antigen in the skin and therefore the possibility of a reverse anaphylactic reaction to the antiserum. He also suggests, if cutaneous and conjunctival tests are negative, a second intravenous test dose of perhaps 3 cc following the conventional 1 cc test dose.

In conclusion, it must be said, regrettably, that neither the skin nor the ophthalmic tests are entirely dependable. A convincing number of cases have been reported in which, despite positive skin reactions, the intravenous administration of serum failed to produce constitutional symptoms of any kind. However, a strongly positive skin reaction, especially with pseudopodia, must be considered as a definite warning signal. Furthermore, a positive ophthalmic test certainly indicates that not only the skin but other tissues also are allergic, and that danger lies ahead.

5. PROPHYLAXIS OF SERUM DISEASE

In a very few diseases is prophylaxis of greater importance than in serum sickness.

¹³¹⁴ DAVIS H M J Hyg 38 325 1938

¹³¹⁵ WALDBOTT G L J A M A 96 416, 1932

The prophylactic methods are divided into four principal groups: (1) avoidance of antitoxins and other serums, if possible; (2) substitution or modification of the serum used; (3) prevention of serum reactions by means of drugs; (4) immunobiologic measures in cases with allergy to serum but urgently requiring antitoxins.

(1) The ideal prophylaxis, and the only one that is completely effective, is to replace antitoxin with toxoid. This, of course, is at present possible only in the case of diphtheria and tetanus antitoxin (Gold,¹³¹⁶ Jones and Moss;¹³¹⁷ Kern and associates¹³¹⁸). In recent years these toxoids have almost completely replaced the serum-containing preparations for preventive immunization. For treatment, however, the toxoids can be used only if the patient has previously received toxoid prophylactically.

According to Gold,¹³¹⁹ it seems safe to give an immunized person a stimulating dose of tetanus toxoid after an injury involving probable infection with tetanus spores, in lieu of an injection of tetanus antitoxin. It should be noted, however, that allergic manifestations following toxoid injections may occasionally occur, although the incidence of untoward reactions appears to be low. Cooke and his co-workers¹³²⁰ first reported on the sensitizing property of alum-precipitated tetanus toxoid and others have since published similar observations. The manifestations vary from anaphylactic shock (Cunningham,¹³²¹ Parish and Oakley¹³²²) to localized brawny swelling at the injection site (Whittingham¹³²³). Other patients present milder systemic reactions characterized by malaise, myalgias, and slight hyperpyrexia, with or without urticaria. It is generally held that the sensitizing agent or agents are Witte and Berna peptone, and to a lesser extent Difco proteose, which are constituents of the culture medium and hence of the toxoid. This was confirmed by the ob-

servation of Long¹³²⁴ that when Witte or Berna peptones were omitted from the tetanus toxoid used by the Army the incidence of allergic reactions fell from 0.05 per cent to less than 1 in 10,000 injections. Edwards' case¹³²⁵ of severe anaphylactoid response appeared to be due to the veal infusion contained in the preparation. The possibility that the bacterial and toxin proteins also act as sensitizing agents cannot be eliminated, but their rôle would seem to be minor.

Sulzberger¹³²⁶ reported a case of chronic urticaria starting 3 days after the first injection of alum-precipitated toxoid and persisting at least 6 months. He presents two possible explanations for this reaction: (1) that the primary sensitivity to proteoses was initiated by the injection and the symptoms maintained by repeated exposure to proteoses in food or of endogenous origin resulting from the catabolism of body proteins; (2) that a small amount of allergen continued to escape over a long period of time from a deposit of the injected toxoid.

Gold¹³²⁷ noted the disparity between the occurrence of positive skin tests and the appearance of symptoms following injection. He concluded that the skin test with toxoid is of no practical value, whether positive or negative, as an indication for or against giving the toxoid. His indifference to the tests is not shared by all (Cooke; Edwards; and others).

Whittingham¹³²⁸ surveyed the reactions among 61,042 subjects in the Royal Air Force immunized with plain tetanus toxoid and found 2 cases of acute anaphylactic shock, 12 of constitutional reactions, and 651 of local reactions. Swartz¹³²⁹ observed 2 cases of urticaria and angioneurotic edema due to fluid tetanus toxoid, 1 with manifestations persisting more than 2 years, and 1 markedly improved after hyposensitization with this substance.

Diphtheria toxoid, both fluid and alum-precipitated, is capable of producing reactions, but appears to do so less frequently than tetanus toxoid. A protamine-precip-

¹³¹⁶ GOLD, H. *ibid* 109: 481, 1937.

¹³¹⁷ JONES, F. G., and MOSS, I. M. *J Immunol* 33: 183, 1937.

¹³¹⁸ KERN, R. A., CRUMP, J., and CORE, T. A. *J Allergy* 6: 525, 1935.

¹³¹⁹ GOLD, H.: *Ann Int Med* 13: 768, 1939.

¹³²⁰ COOKE, R. A., HAMPTON, S. F., SHERMAN, W. B., and STULL, A. *J A M A* 114: 1354, 1940.

¹³²¹ CUNNINGHAM, A. A.: *Brit. M J* 2: 522, 1940.

¹³²² PARISH, H. J., and OAKLEY, C. L.: *ibid* 1: 294, 1940.

¹³²³ WHITTINGHAM, H. E.: *ibid.* 1: 292, 1940.

¹³²⁴ LONG, A. P. *Am J Pub Health* 33: 53, 1943.

¹³²⁵ EDWARDS, W. M. *J Allergy* 14: 532, 1943.

¹³²⁶ SULZBERGER, M. B. *U. S. Nav M Bull* 40: 413, 1942.

¹³²⁷ GOLD, H. *J Lab & Clin Med* 27: 26, 1941.

¹³²⁸ SWARTZ, H. *J Allergy* 14: 544, 1943.

tated diphtheria toxoid has been produced, and, according to preliminary reports, gives rise to practically no reactions

(2) Despeciated tetanus antitoxin should be administered to persons who have not previously been actively immunized with tetanus toxoid or to patients presenting clinical evidence of tetanus. The same holds true in relation to diphtheria, scarlet fever, and gas gangrene. In these preparations, the horse serum has been so changed immunologically by partial digestion with taka diastase that allergic reactions are minimal (Coghill and associates¹³⁷⁹). This was confirmed in regard to despeciated tetanus antitoxin by Schaeffer and Myers,¹³⁸⁰ to scarlet fever antitoxin by Toomey and Kimball, and to diphtheria antitoxin by Baird. While immediate reactions were not observed by Top and Watson,¹³⁸¹ serum sickness occurred in 18 per cent of their cases on the sixth day.

Edwards¹³⁸² has found that bovine serum can be made safe for man by destroying the antibodies by heating to 72 C., after which it was possible to administer it safely in large amounts as a substitute for human plasma.

Another method consists in the use of protein-poor and purified serums. These preparations have the advantage of containing the required quantity of antibodies in about the smallest possible volume of serum, having been freed of all protein fractions other than those serving as the antibody carriers. Northrop has recently reported on a purified antitoxin that he claims to be forty to fifty times more effective than the crude form, and that apparently does not evoke serum reactions. Poehacker, Fritsch and Siegl¹³⁸³ worked with "fermo" serum in which the proteins having no antitoxic effect are removed by fermentative decomposition. It requires five hundred times the dose of this preparation to produce the same allergic reaction as that elicited by the unchanged globulin.

As this brief review indicates, the future of

prophylaxis in serum sickness is quite encouraging. The main lines of further investigation seem to lie in the direction of the use of toxoids or of despeciated and purified serums.

Among the prophylactic measures of secondary importance, mention may be made of the use of a serum (e.g. bovine, rabbit, chicken) to which a known horse serum sensitive patient does not react. Thus, Glaser¹³⁸⁴ 1935 found that the incidence of moderate generalized reactions was markedly less and of alarming reactions practically nil when bovine tetanus antitoxin was employed, as compared to equine antitoxin. Moreover, it would be feasible to use heterologous serums for different purposes—as, for example, prophylactic inoculation with diphtheria or tetanus immune serum from a steer, sheep, goat, or rabbit, while the corresponding immune serum from a horse is employed in therapy. Since other animals than the horse do not achieve high antibody titer, it is necessary to inject larger amounts of their serum and this in turn may bring on severe allergic reactions. Human tetanus antitoxin, which can be produced by immunizing subjects with toxoid (Glaser¹³⁸⁴), has been tried. It is also possible to take advantage of the principle of passive serum sickness by employing the serum from individuals who have recently recovered from serum sickness according to Voss and Hundt,¹³⁸⁵ such convalescent serum, given early in the incubation period of serum sickness, is followed only by an immediate small local reaction, and prevents serum disease (see pp 90 and 354).

Finally, Kahn¹³⁸⁶ recommends that prophylactic and therapeutic serum be given not subcutaneously but intramuscularly, pointing out that the antigen localizing capacity of the cutaneous tissue is approximately ten times as great as that of skeletal muscle tissue. This will of course considerably reduce the likelihood of sensitization.

(3) On the hypothesis that the phenomena of serum sickness are due to a release of histamine or a histamine like substance, Foshay and Hagebusch⁴³⁴ as well as Cherry and Prickman,⁴³⁵ treated patients both orally and

¹³⁷⁹ COGHILL, R. D., FELL, N., CREIGHTON, M., and BROWN, G. *J. Immunol.* 39: 207, 1940.

¹³⁸⁰ SCHAEFFER, M., and MYERS, G. B. *J. Allergy* 12: 188, 1941.

¹³⁸¹ TOP, T. H., and WATSON, E. H. *Am. J. Dis. Child.* 62: 548, 1941.

¹³⁸² EDWARDS, F. R. *Brit. M. J.* 1: 23, 1944.

¹³⁸³ POEHACKER, FRITSCH, E., and SIEGL, J. *Wien. Klin. Wochenschr.* 54: 391, 1941.

¹³⁸⁴ GLASER, J. *J. Allergy* 12: 537, 1941.

¹³⁸⁵ Idem. *New York State J. Med.* 42: 1080, 1942.

parenterally with histaminase before administering the serum, and claim very good results. However, Toomey et al⁴⁷ and Eger and Stone⁴⁸ in well-controlled clinical experiments found that histaminase neither prevents nor ameliorates serum sickness.

It has been suggested that an injection of epinephrine hydrochloride just prior to the serum injection and ephedrine sulfate orally every three or four hours for 3 to 5 days thereafter may minimize serum reactions.

According to Faraglia, intravenous injection of a solution of 0.5 Gm. of calcium gluconate in 5 cc. of double distilled water fifteen minutes prior to an intramuscular injection of tetanus antitoxin prevents anaphylactic reactions. The same claim is made by Stout and Kositchek for intravenous use of 50 per cent dextrose.

(4) In patients known to be hypersensitive to horse serum but urgently requiring serum therapy, the skeptophylactic method of Besredka³⁹⁷ should be employed. The procedure consists of administering the serum in slowly and gradually increasing doses, with intervals of twenty minutes between injections. The amounts to be given, as well as the rate, depend upon the degree of the patient's hypersensitiveness. For example, a severe case, presenting positive skin and ophthalmic tests, would best be treated by the schedule in Table 34; while less severe cases (positive skin but negative ophthalmic tests) admit of certain modifications, as for example, a concentration of 1:10 in the initial intravenous injection.

The following precautions should always be kept in mind. Subcutaneous injections should be given only in the extremities, so that a tourniquet can be applied if necessary. In areas that cannot be controlled by a tourniquet, epinephrine should be injected subcutaneously when the possibility of an allergic reaction is suspected on the basis of the history. In what appear to be dangerous cases, 0.1 cc. of epinephrine may be mixed with the serum and administered with every injection, as long as the injections are performed subcutaneously. But even in the routine case it may be advisable to administer 0.2 cc. of epinephrine with the initial injection. When untoward manifestations, such as apprehension, erythema, urticaria, precordial distress, or

dyspnea arise, the administration of serum should be stopped and 1 cc. of an epinephrine solution should be injected intramuscularly. In the event of alarming reactions, it is necessary that 0.2 to 0.4 cc. of diluted epinephrine solution be injected intravenously. After the allergic manifestations have disappeared completely, the injections may be resumed, commencing with a dose equivalent to one-half or less of the previous dose. As an added pre-

TABLE 34—Method of Deallergization of Patient Allergic to Foreign Serum

Frequency of injections 1 every 20 minutes

Dose No	Quantity (Cc)	Concentration	Route
1	0.05	1:10	subcutaneous (deep)
2	0.1		
3	0.3		
4	0.7		
5	0.1	undiluted	
6	0.3		
7	0.7		
8	0.1	1:100	intravenous
9	0.3		
10	0.7		
11	0.1	1:10	
12	0.2		
13	0.4		
14	0.8		
15	0.1	undiluted	
16	0.2		
17	0.4		
18	0.8		
19	1.0		
20	3.0		
21	7.0		
22	10.0		

caution, a tourniquet should be in place above the site of injection, ready to be tightened at the first sign of a reaction.

Besredka's method was found by Borisenko-Mitlash and Popov^{173a} to be quite reliable in the prophylaxis of severe and fatal anaphylactic shock following administration of large amounts of antitangrene serum by intramuscu-

^{173a} BORISENKO-MITLASH, and POPOV, V. I. — *Khirurgiya* 2-7, 1945.

lar intraperitoneal and subdural injection and somewhat less so with respect to intra venous infusion of large doses of heterogenous serum. Their method consisted of injecting a small amount of serum intramuscularly one and one half to two hours previous to the infusion. Prophylaxis was enhanced by simultaneous narcosis with evipal along with injection of ephedrine.

Finally there is the intravenous drip method. Hirshfield³³⁶ has shown that anaphylaxis fails to appear in sensitized animals when the antigen is injected intravenously very slowly and in very high dilutions. This is probably attributable to the fact that a certain minimum concentration of antigen must reach the blood within a certain very brief span of time in order to evoke an anaphylactic shock. Vaughan² recommends this continuous venoclysis as an alternative method on the grounds that the schedule outlined above, requiring some twenty five to thirty injections most of which must be intravenous is extremely time consuming for the physician and most annoying to the patient. Another advantage is that the intravenous route is used exclusively the absorption of serum following subcutaneous or intramuscular injection being rather slow and therefore not especially effective.

TECHNIC. The burette is filled with 100 cc of a 1:1000 dilution of the serum in physiologic saline solution. At least one hour is allowed for the introduction of this amount which corresponds to 0.1 cc of undiluted serum. The patient is then given 100 cc of a 1:100 solution at the same rate this corresponding to 1 cc of undiluted serum. Following this the undiluted serum is injected with a syringe according to the following schedule: the intervals between injections being thirty minutes: 0.2 cc, 0.4 cc, 0.8 cc, 1.6 cc, 3.2 cc, 6.4 cc and 12.8 cc. Thereafter the entire amount may be given.

While the fear of possible serum reactions should never deter the administration of serum to a patient who really requires it the physician should bear in mind the fact that there have been more deaths or at least more severe anaphylactic reactions following serum injections than the medical textbooks generally admit.

6 TREATMENT OF SERUM DISEASE

Once serum sickness has developed there are no methods of cutting short the course of the disease. However the symptoms can be influenced. The distressing pains may be alleviated by large doses of salicylates. The intense itching can be controlled for a few hours by ephedrine sulfate (0.045 Gm or $\frac{3}{4}$ grain three times a day) or if necessary by injections of epinephrine (0.5 cc of a 1:1000 solution). Slow acting epinephrine (1 cc of a 1:500 suspension in oil intramuscularly) may be used to reduce the frequency of the injections required. Local application of a 2 per cent calmitol lotion is often helpful.

R _x	Gm or Cc	gr xxx
Calmitol	2 0	
Zinc oxide		
Talc	aa 20 0	aa 3 v
Glycerin		
Alcohol 70%	aa 30 0	aa 13 i

M Sig. Shake and apply locally every 3 hours

If the patient's condition permits starch baths to which 5 cc (1 dram) of a 25 per cent solution of menthol in alcohol is added are frequently effective in alleviating the pruritus.

Furthermore a trial of intravenous calcium is warranted. Kantzky reported good results obtained by the energetic application of diaphoresis. The patient remains in a luminous heat cabinet for twenty minutes at 60 to 70 C the optimal temperature for this purpose. In order to increase the secretion of sweat the patient is given a pint of hot tea to drink just before entering the box.

The treatment of anaphylactic shock is discussed in detail on page 485.

E THE Rh FACTOR

The brilliant investigations of Landsteiner, Wiener, Levine, Davidsohn and others have firmly established the clinical significance of the Rh blood factor in the causation of intra group transfusion reactions as well as of fetal erythroblastosis. A voluminous literature on this subject has arisen in a very few years and cannot be considered in detail here. Like the agglutinogens responsible for the blood groups A, B, AB, M and N the Rh factor is present in the red blood cells of many human beings and under certain circumstances will give rise to the clinical manifesta-

tations mentioned. They constitute examples of isoimmunity or, better, isosensitivity. In so far as the isosensitization and the subsequent reactions result from blood transfusions, the discussion is pertinent to this chapter on injectants. However, while sensitization may occur by reason of repeated pregnancies under appropriate conditions, and while fetal manifestations also take place without the intervention of injections, these phenomena may be conveniently considered here, since they are so closely allied to that above. Recent reviews on the subject of the Rh factor have been contributed by Wiener^{1227, 1228} and Levine.¹²²⁹

In its simplest terms, an agglutinin is a specific antigen occurring in the red blood cells and an agglutinin is the specifically related circulating antibody; their interaction is manifested by agglutination (or hemolysis) of the erythrocytes, and, when it occurs in the body, by subsequent clinical sequelae.

In 1940, Landsteiner and Wiener¹²³⁰ discovered in the blood of rhesus monkeys—hence the designation “Rh factor”—an agglutinin which when injected into rabbits or other animals produces a specific antiserum. This was found by Levine et al.¹²³¹ to be capable of agglutinating the bloods of about 85 per cent of white human beings regardless of their sex or blood types, and these individuals are said to be Rh positive, while the remaining subjects whose erythrocytes are not clumped by such serums are called Rh negative. The Rh factor is a permanent and static constituent of blood, inherited as a mendelian dominant characteristic (Landsteiner and Wiener¹²³²). However, the Rh antibodies or agglutinins, unlike the α and β -agglutinins, are normally absent from the blood and when present are always due to immunization; they are therefore subject to many influences affecting sensitization.

Transfusion of Rh positive blood into an Rh negative individual may stimulate the formation of Rh antibodies or agglutinins, although actually repeated transfusions are required. The serum from such patients is called anti Rh serum, or Rh immune serum, or Rh antiserum. Rh negative subjects vary in the ease with which they can be sensitized: perhaps 1 in 25 or 50 are readily immunized by repeated exposure to the Rh antigen.

Wiener and Peters¹²³³ showed in 1940 that hemolytic transfusion reactions may be due to this mechanism, and since that time this observation has been confirmed. It has been estimated (Wiener¹²³⁴) that about 90 per cent of intragroup hemolytic transfusion reactions (i.e., those caused by bloods compatible by ordinary blood grouping and cross-agglutination methods) are due to Rh isoimmunization, resulting from repeated transfusions or recent pregnancies. Reactions are usually mild at first (slight chilliness or hyperpyrexia), but become progressively more severe as transfusions are repeated, until a violent or even fatal hemolytic reaction will ensue. Since at least 5 to 7 days and usually longer are required for sensitivity to develop, transfusions given at short intervals will not produce this complication. Patients who have exhibited even a mild reaction should be studied for the Rh factor to prevent a more dangerous one should further transfusion become necessary. Transfusions of either Rh positive or Rh negative blood into an Rh positive individual of either sex (except infants with fetal erythroblastosis) are harmless and the donors need not be Rh tested. It is evident that Rh negative individuals should receive only Rh negative blood, particularly if repeated transfusions are contemplated, or if the patient is a woman with previous pregnancies or a prospective mother. In view of this consideration, the only “universal” donor may now be taken to be one of type O, Rh negative, and with a low titer of isoagglutinins.

Isoimmunization may also take place, in the absence of transfusions, in the pregnant woman, provided she is Rh negative and the fetus Rh positive, the latter characteristic

¹²²⁷ WIENER, A. S. *Blood Groups and Transfusion* 3d ed Springfield, Ill. Thomas, 1943.

¹²²⁸ WIENER, A. S. *Ann. Allergy* 3, 229, 1945.

¹²²⁹ LEVINE, P. J. *J. Pediatr.* 23, 656, 1943.

¹²³⁰ LANDSTEINER, K., and WIENER, A. S. *Proc. Soc. Exper. Biol. & Med.* 43, 223, 1940.

¹²³¹ LEVINE, P., VOGEL, P., KATZIN, E. M., and BURNHAM, L. *Science* 54, 371, 1941.

¹²³² LANDSTEINER, K., and WIENER, A. S. *J. Exper. Med.* 74, 309, 1941.

¹²³³ WIENER, A. S., and PETERS, H. R. *Ann. Int. Med.* 12, 2306, 1940.

¹²³⁴ WIENER, A. S. *Am. J. Clin. Path.* 15, 106, 1945.

inherited as a mendelian dominant from the father (Levine Katzin and Burnham¹³⁴). The fetal Rh antigen is presumed to reach the maternal circulation by transplacental passage with resulting production of anti Rh agglutinins in the maternal organism. Just how this happens is uncertain but placental defects are often found in such cases (Javert¹³⁵) or possibly merely breakdown products of physiologic fetal red blood cell destruction pass through the placental barrier.

Without going too deeply into the genetics it is necessary to consider whether the parents are homozygous with regard to this factor carrying two determinant genes (genotype RhRh) or heterozygous (Rhrh) being Rh positive in either case. Since the factor is a dominant characteristic the Rh negative individual must be homozygous (rhrh). All the offspring of a homozygous Rh positive mother or father must be Rh positive irrespective of the spouse's type. However mating of an Rh negative mother with a homozygous Rh positive father will result in all Rh positive children and with a heterozygous father in an estimated 50 per cent of Rh positive children thus giving rise to the circumstances permitting isosensitization of the mother. A heterozygous mother will have all or a portion of her children Rh positive depending on the father's genotype but no isoimmunization can develop since she is already Rh positive. Finally when both parents are Rh negative all offspring must be likewise. In brief isosensitization results only when the mother is Rh negative the father is Rh positive and the fetus is Rh positive.

The titer of maternal anti Rh agglutinins under these conditions is highest 8 to 20 days after delivery and may persist for long periods or disappear rapidly from the circulation (Davidsohn¹³⁷) although Levine^{134b} stated that sensitization is probably retained throughout life and Young and Karber¹³⁹ found it to persist for at least 8 to 16 years respectively in two cases and others for periods varying

from 9 to 23 years. Such a sensitized female will exhibit transfusion reactions to the first infusion of Rh positive blood while it is obvious that males and nulliparous females can not do so. The high titer serums of certain such mothers are best used for Rh testing and may be obtained from several sources although some animal serums especially from immunized guinea pigs have been successfully employed. The degree of sensitization usually progresses with each pregnancy with an Rh positive fetus although it need not. Anti Rh agglutinins found in a gravid woman may have persisted from a previous pregnancy and have nothing to do with the fetus in utero at the time of the examination.

Convincing evidence attributes the etiology of fetal erythroblastosis to a mechanism involving the Rh factor. Given the circumstances outlined above resulting in isosensitization of the gravid female it is postulated that the anti Rh agglutinins reach the fetus through the placenta. The permeability of the human placenta to hemagglutinins and other antibodies has been demonstrated by Wiener and Silverman¹⁴⁰ and others. As a consequence the fetal organism contains both the antigen (the Rh factor) and the antibody passively acquired from the mother. Hence an antigen antibody response occurs in the fetus and hemolysis ensues with a resultant pathologic sequence of events leading to the clinical and pathologic findings of the disease.

Numerous observations have confirmed this concept of the mechanism of fetal erythroblastosis. The combination of Rh positive father and baby and Rh negative mother is found in about 90 per cent of the cases in marked contrast to the distribution in the general population and anti Rh agglutinins are demonstrable in the mother as a rule. However these tests are not in themselves diagnostic of the disease since other conditions may simulate the clinical and hematologic findings of fetal erythroblastosis (Davidsohn¹³⁵). Moreover the presence of a great amount of Rh agglutinins in the serum of a pregnant woman need not mean that the infant will exhibit clinically demonstrable

¹³⁴ LEVINE P. KATZIN E. M. and BURNHAM L. P. *Proc So Exptl Biol & Med* 45: 343 1930

¹³⁵ JAVERT C. T. *Am J Obst & Gynec* 43: 921 1942

¹³⁶ DAVIDSOHN I. *Am J Clin Path* 15: 95 1941

¹³⁷ LEVINE P. A. *h Pa* 37: 83 1944

¹³⁸ YOUNG L. E. and KARBER D. H. *J A M A* 127: 627 1945

¹³⁹ WIENER A. S. and SILVERMAN I. J. *J Exptl Med* 1: 2 1940

¹⁴⁰ DAVIDSOHN I. J. A. M. A. 127: 633 1945

erythroblastosis (Dockeray and Sachs^{124c}). In about 10 per cent of cases of fetal erythroblastosis the mothers are Rh positive. These may be largely explained by isoimmunization against Rh subtypes, and the Hr factor, while rare cases appear to be due to isoimmunization against common blood group factors A, B, and possibly even M and P. This last possibility was proved with respect to isoimmunization with the A antigen in 9 cases studied by Polayes and Ohlbaum.^{125a} Instances have been reported of bi-ovular twins, one being Rh positive and having hemolytic disease of the newborn, the other being Rh negative and free of disease (Potter; Kariher).

Although families with Rh negative mothers and Rh positive fathers and infants occur with a frequency of about 9 or 10 per cent in the population, hemolytic disease appears in only 1 out of 250 to 500 births. This is probably accounted for by differences in the permeability of the placenta and in the capacity of mothers to become sensitized. About 1 in 25 or 50 females are readily sensitized, the remainder require 10 to 20 or more transfusions or pregnancies—circumstances not frequently occurring. Erythroblastosis is quite rare in the first born.

It has been repeatedly suggested that the term "hemolytic disease of the fetus and newborn" be used instead of fetal erythroblastosis, since erythroblastosis is merely one of the findings and not always a prominent one, while hemolysis is an essential feature. The pathologic picture includes hemolytic anemia, erythroblastemia, icterus gravis, and congenital hydrops (Davidsohn^{125b}). The relationship of these to the underlying mechanism is illustrated in FIGURE 161. About 50 per cent of cases die before they are 7 days old. Late sequelae include juvenile cirrhosis, kernicterus, and probably, as indicated by the investigations of Yannet and Lieberman,^{125c} some undifferentiated severe mental defects.

Recognition of the etiology of fetal erythroblastosis has given rise to rational therapy—repeated transfusions with Rh negative blood

free from agglutinins, or if this is not available, with the mother's twice washed erythrocytes, if compatible, suspended in saline or compatible plasma, along with oxygen to combat the anoxemia. In Javert's series^{124e} the death rate was reduced from 73 to 14 per cent. It has been shown that Rh positive red blood cells are destroyed and disappear rapidly (within 5 days) from the circulation, until such time as the hemolytic process ceases. In some severe instances, all the red cells in the circulation for a period of one month have been demonstrated to be those given by transfusion. Erythroblastotic infants should not be nursed since the Rh isoantibodies are secreted in the mother's milk.

Once a mother has given birth to an infant with erythroblastosis, all subsequent fetuses will exhibit the disease provided they are Rh positive. Factors of possible significance with regard to future pregnancies are the homozygosity or heterozygosity of the husband, if determinable, and the persistence of anti Rh agglutinins in the mother's blood (Davidsohn¹²⁷). Heterozygosity can be established in some instances by finding that a parent, a sibling, or a child of an Rh positive person is Rh negative. The obstetric histories of mothers of erythroblastotic infants not infrequently include previous spontaneous abortions and stillbirths, although present evidence permits no conclusions regarding the importance of the Rh factor in repeated spontaneous abortions and multiple stillbirths (Walsh^{126a}).

Rh subtypes, based on reactions with human anti Rh agglutinins, have been demonstrated. The most common anti Rh agglutinin, giving reactions parallel with standard anti-rhesus agglutinin, is known as anti Rh₀. Two other varieties of human anti Rh agglutinins have been recognized: the anti Rh' reacts with about 70 per cent of bloods from white individuals, the other, anti Rh'', with about 30 per cent. By means of these three varieties of Rh isoagglutinins, 8 types of human blood can be differentiated; all of these but the rarest type (Rh'Rh'') with a calculated frequency of only 1 in 10,000 have actually been encountered. Their designations, reactions with antisera, and distributions in white

^{124c} DOCKERAY, G. C., and SACHS, H. *J. Immunol.* 48: 244, 1944

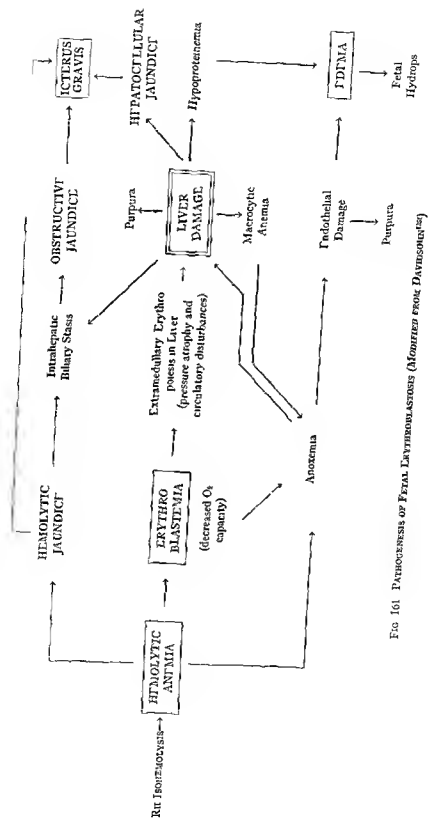
^{125a} POLAYES, S. H., and OHLBAUM, C.: *Am. J. Clin. Path.* 15: 467, 1945

^{125b} DAVIDSOHN, I.: *M. Clin. North America* 28: 232, 1944

^{125c} YANNET, H., and LIEBERMAN, R.: *J. A. M. A.* 130: 335, 1946

^{126a} WALSH, R. J.: *M. J. Australia* 2: 33, 1945

ALLERGY

FIG 161 PATHOGENESIS OF FETAL ERYTHROBLASTOSIS (MODIFIED FROM DAVISON¹⁵²)

and Negro groups will be found in Table 35. Mestizo people, American Indians, Negroes, Chinese, Japanese, Indonesians, and Australian aborigines are characterized by virtual absence of the Rh negative type and hence of fetal erythroblastosis.

The recognition of these blood types has medicolegal application as regards identification of individual blood specimens and in cases of disputed parentage. Along with blood groups O, A, A₁, A₂, B, A₁B, A₂B, P, M, N, and MN, 288 varieties of blood can be detected, and the chances of proving non-paternity are enhanced about 16 per cent (Wiener¹³⁴⁴).

TABLE 35—The Eight Rh Blood Types and Their Distribution (Wiener^{1344 1325})

Designation of Types	Bloods Lacking Rh ₀ Factor					
	Reactions with Antiserums			Distribution (per cent)		
	Anti Rh ₀	Anti Rh	Anti Rh ⁺	Whites	Negroes	
Neg	—	—	—	12.9	8.1	
Rh ⁺	—	+	—	0.9	2.2	
Rh ⁺	—	—	+	0.3		
Rh ⁺ /Rh ⁺	—	+	+	0.01		
	Bloods Containing Rh ₀ Factor					
	Rh ₀	+	—	—	2.6	41.7
	Rh ₁ (Rh ⁺)	+	+	—	54.1	20.2
	Rh ₂ (Rh ₂)	+	—	—	12.8	22.4
	Rh ₁ Rh ₂ (Rh ₁ Rh ₂)	+	+	+	16.4	5.4

The technic of Rh testing need not concern us here. It may be noted, however, that as yet the only Rh antibodies discovered are agglutinins, although clinically hemolysis takes place. These are "warm" agglutinins, reacting best at body temperatures, unlike the anti-A and anti-B agglutinins (Davidsohn¹³⁴⁷); this may reflect the fact that the latter are among the so-called normal antibodies, not due to parenteral immunization. It should also be pointed out that in vitro tests for anti Rh agglutinins are not positive in a high percentage of persons with Rh negative blood who are highly reactive to the Rh factor, and that there exists a "prozone phenomenon" in which undiluted anti Rh serums fail to react while bigger dilutions do. Moreover, anti

Rh agglutinins may not be demonstrable by the usual methods (or only in traces) in some Rh negative mothers of erythroblastotic infants. This failing is reported to be largely obviated by the rapid slide method of demonstrating anti Rh agglutinins (Diamond and Abelson¹³⁵⁵). All of these phenomena may be accounted for by the presence of the blocking antibodies discovered by Wiener.¹³⁵⁶ These are conceived as being a counterpart of the haptens, capable of combining with the red blood cells though not of agglutinating them, and interfering with agglutination by Rh antibodies. The blocking antibody so far found invariably gives reactions corresponding to anti Rh₀.

Because of these and similar technical difficulties with in vitro methods of determining Rh incompatibility,* Wiener et al.^{727, 728} have devised a simple biologic test which can be done at the bedside. The patient's blood is drawn before and again one to one and one-half hours after the intravenous injection of 50 cc. of the citrated blood of the prospective donor. If the serum or plasma of the second specimen is detectably darker than that of the pre-injection one, or if there is a distinct rise in the icterus index even though it remain within normal limits, hemolysis has occurred and the blood should not be used for the transfusion. Not infrequently clinical symptoms such as a chill or fever accompany the reaction, but cannot be depended upon since they may be quite mild or entirely absent, or may not appear until later. If the reaction is negative, any quantity of blood from the same donor may be given. If the difference in color is questionable, the test may be repeated. It is recommended that this precaution be followed before giving blood to any Rh negative patient, particularly pregnant women or prospective mothers, cases of purpura, and those receiving repeated transfusions.

The commonest cause of intragroup incompatibility in Rh positive individuals, as well as an explanation of some of the 10 per cent of cases of fetal erythroblastosis in which

¹³⁵⁵ DIAMOND, L. K., and ABELSON, N. M. J. Lab. & Clin. Med. 30: 201, 668, 1945.

¹³⁵⁶ WIENER, A. S. Proc. Soc. Exper. Biol. & Med. 56: 173, 1944.

* It must be emphasized that, for several reasons, routine cross-agglutination tests are also inadequate in this respect.

the mother is Rh positive, lies in the Hr factor (Levine et al.¹³⁵⁷) This gives rise to a rare atypical agglutinin developing in Rh positive persons and clumping the blood of all Rh negative persons, as well as some Rh positive. The existence of the anti Hr agglutinin has been confirmed, and some immunologists claim that such serum can be used to determine the heterozygosity of males, but this point is still disputed.

F INSECT BITES AND STINGS

Logic demands that insect bites and stings be included among the parenteral injectants. The cutaneous and constitutional reactions that follow them may be due to toxicity (i.e., to the primary toxic action of the insect's secretion, as, for example, the poison of the bee), or to a hypersensitiveness to insect protein introduced into the body by the bite or sting. It surely cannot be denied that there are numerous instances in which toxic substances enter the organism as a result of the bite, followed by more or less severe local and even general symptoms. However, there have certainly been enough observations of the other kind—cases in which an underlying allergic mechanism was demonstrated beyond question. It is known to be possible to allergize human beings by allowing them to be bitten by flies, fleas, and other insects at intervals of several days (Hecht, Boycott). Moreover, it has been observed many times that the first bite or sting causes nothing more than a mild local reaction, while after a number of them the subject reacts with several local and some times even general manifestations. This sequence was confirmed by the careful experimental studies of Peck, Wright, and Gant¹³⁵⁸ on bites of the body louse. Repeated exposure to bites resulted in the development of dermal hypersensitiveness to them in the majority of subjects. Contrary to previous opinion, the feces of the louse played an important part in this induced reaction. There are apparently two components to the "louse bite reaction"—the purpuric element due to the trauma of the act of feeding, and the de-

velopment of an inflammatory reaction following sensitization requiring an incubation period of about seven days and sometimes leading to severe, even generalized dermatitis. The pruritus accompanying pediculosis seems to depend largely on the existence of hypersensitiveness.

The experiments of these authors may also apply to a larger field—the eczematoid lesions observed in scabies and other mite infestations. Most of the dermatitides in scabetic patients are undoubtedly the result of treatment, mechanical irritation, or exacerbation of existing seborrheic dermatitis. Some instances, however, cannot be explained on such a basis, and suggest specific sensitization to the mite or some of its products. Dermatitis in workers unloading imported cheese infested with mites of the *Tyroglyphus* family, which is also known to be responsible for eruptions in handlers of dried coconut kernels, was reported by Dowling and Thomas.¹³⁵⁹ Except for a few small urticarial lesions on the fore arms of one patient, the eruption in no case suggested a parasitic cause but was characteristic of a dermatitis. In the light of the above experiments on lice, one might explain the urticarial lesions as primary toxic effects of the mite bites and the dermatitis as a phenomenon of sensitization.

Additional proof of the allergic nature of these reactions to insect bites and stings is based on both natural and artificially induced hypsensitization resulting from repeated bites or from injections with insect extract. Thus Stokes¹³⁶⁰ and other authors have pointed out that natives in countries infested with the black fly very frequently acquire a high degree of immunity to this insect, while white immigrants manifest severe reactions. Further more, the susceptibility to the bite of bed bugs manifested by Americans traveling on the Continent, is well known. There is a higher incidence of insect dermatoses among children than among adults. Some persons develop a season's immunity in about ten days, but react again, although less violently, the following season. The immunity of indigenous cattle has long been recognized

¹³⁵⁷ LEVINE P, BURNHAM L, KATZIN E and VOGEL P. *Am J Obst & Gynec* 42: 925 1941.

¹³⁵⁸ PECK S M, WRIGHT W H and GANT J Q. *J A M A* 123: 821 1943.

¹³⁵⁹ DOWLING G B and THOMAS E W. *P. Brit M J* 2: 543 1942.

¹³⁶⁰ STOKES J H. *J Cutan Dis* 32: 251 1914.

Ellis and Ahrens,¹³⁶⁴ Fisher,¹³⁶¹ Benson and Semenov,¹³⁶² McLane,¹³⁶³ and others have reported successful hyposensitization with bee extract, Benson¹³⁶⁴ with mosquito extract, McIvor and Cherney¹³⁶⁵ with flea extract, Morrow¹³⁶⁶ with chigger extract, and Mease¹³⁶⁷ with deer fly extract. That the antigenic substance is of protein origin was indicated, if not proved, by Ellis and Ahrens,³⁹¹ who showed that a saline extract of bee substance that had been subjected to tryptic digestion failed to elicit reactions. According to Benson¹³⁶⁴ individuals hypersensitive to mosquito react to extracts of both male and female mosquitoes. Since the male of this species does not sting or produce venom, reactions to the male extract lend strong support to the assumption that the allergy is in relation to mosquito protein.

Allergic reactions are known to occur from bites or stings of bees, wasps, horseflies, flies, gnats, mosquitoes, fleas, lice, and bedbugs. The most dangerous of these is bee sting allergy. A report by Braun¹³⁶⁸ illustrates the proportions this particular allergy can assume: whenever his patient was stung by a bee, her entire body, including the face, became red within one minute; this was followed by diffuse swelling. The patient felt as though she were suffocating and was also distressed by persistent coughing. There were intense cramps in the abdomen, like labor pains. There was marked apprehensiveness and depression, together with trembling of the whole body, followed by a coma-like condition. Commencing at the site of the sting, generalized urticaria spread over the entire body. Obermayer's¹³⁶⁹ report of a severe systemic reaction within ten minutes following a bee sting is of interest in that the local lesion was not impressive. Helms¹³⁷⁰ case had the manifestations of severe anaphylactic shock, including an imperceptible radial pulse and unobtainable

blood pressure, while Jex-Blake¹³⁷¹ described two cases with fatal termination within two and fifteen minutes respectively.

Ludwig¹³⁷² reported an anaphylactic shock that he himself suffered after a wasp sting, five weeks previously, a similar sting had evoked no allergic reaction whatever. He had probably been allergized by that first sting. Duke¹³⁷³ described the sudden death of a child

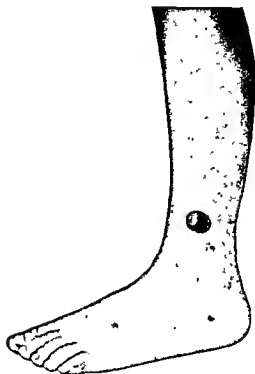


FIG 162. HYPERSENSITIVENESS TO INSECT BITE (FLEA) CAUSING BULLOUS LESION

following the sting of a wasp, he¹³⁷⁴ also observed a case of hypersensitivity to the bite of the common horsefly. Brown and his associates³⁹⁰ reported the unique case of a young girl with local anaphylaxis (Arthus phenomenon) following each mosquito bite. Systemic manifestations resulting from extreme sensitivity to the sting of "yellow jackets" were seen by Lincoln¹³⁷⁴ and Owen.¹³⁷⁵ Asthma fol-

¹³⁶¹ FISHER, D. C. *J. Allergy* 5: 519, 1934

¹³⁶² BENSON, R. L. and SEMENOV, H. *ibid.* 1: 105, 1930

¹³⁶³ McLANE, E. G. *Minnesota Med.* 26: 1061, 1943

¹³⁶⁴ BENSON, R. L. *J. Allergy* 8: 47, 1936

¹³⁶⁵ McIVOR, B. C., and CHERNEY, L. S. *Am. J. Trop. Med.* 23: 37, 1943

¹³⁶⁶ MORROW, A. S. *Proc. Soc. Exper. Biol. & Med.* 45: 303, 1940

¹³⁶⁷ MEASE, J. A. *J. A. M. A.* 122: 227, 1943

¹³⁶⁸ BRAUN, L. *South African M. Rec.* 23: 105, 1925

¹³⁶⁹ OBERMAYER, M. E. *Arch. Dermat. & Syph.* 51: 6, 1945

¹³⁷⁰ HELMS, S. *Wid. Surgeon.* 92: 64, 1943

¹³⁷¹ JEX-BLAKE, A. *J. Brit. M. J.* 2: 241, 1942

¹³⁷² LUDWIG, M. *Arch. f. Klin. u. Exp. Derm.* 81, 1934, 1934

¹³⁷³ DUKE, W. W. discussion to Figley, 1931

¹³⁷⁴ LINCOLN, M. *J. Allergy* 7: 372, 1936

¹³⁷⁵ OWEN, G. W. Letters, Internat. Corr. Club of Allergy.

lowing flea bites and even injections of flea antigen was reported by McIvor and Cherney,¹³⁶⁵ and from bedbugs by Sternberg¹³⁷⁶ Lahoz and Recatero,¹³⁷⁷ and Jimenez Diaz and Sanchez Cuenca¹³⁷⁸

Less severe but still sufficiently disagreeable urticarial and even bullous reactions (Fig 162) have been observed in individuals hypersensitive to fleas and bedbugs

There is no reason to think that the toxic manifestations resulting from the bite of the black widow spider are on an allergic basis

The allergic skin responses to insect bites and stings may appear either in the form of immediate wheal reactions or as the late twenty four hour papular tuberculin type response. The former is the more common manifestation of cutaneous allergy to the products of insects, particularly mosquitoes. The late reaction is more typical of the response to bedbugs. In a series of experiments Hecht succeeded in evoking both types of reaction and is of the opinion, therefore, that they are both of allergic origin

As regards treatment, it should be mentioned that hyposensitization appears to depend on the type of reaction in the given case, it has been successful in cases presenting the late response, while as a rule the urticarial forms of hypersensitiveness cannot be satisfactorily influenced (Benson¹³⁷⁹, Sulzberger⁴). The acute systemic symptoms are usually controlled by epinephrine by injection or epinephrine by mouth, although intravenous calcium is often helpful. Shannon¹³⁸⁰ has found that administration of thiamin chloride markedly reduces the severity and persistency of the wheals from mosquito bites

Although not strictly pertinent to this section, the question of hypersensitiveness to catgut may be briefly mentioned here

Henry¹³⁸¹ considered the possibility that one cause of postoperative evisceration may be a local allergic reaction to chromic catgut leading to unduly rapid absorption, and supported his thesis not only with histologic evidence, but also by obtaining a positive skin test with an extract of chromic catgut in one such case. The patients are thought to be sensitized by reason of previous operations, previous protein therapy, or treatment with sheep serum. Hinton^{1381a} had earlier suggested that delayed healing and dehiscence of surgical wounds in the absence of infection may result from catgut allergy, and that as a consequence incisional hernia or recurrence of hernia after repair may ensue. He found that about 8 per cent of a series of preoperative patients reacted to an extract of fresh sheep gut. Babcock^{1381b} studied the tissue reactions to catgut by burying short sections in the sterilized skin, although there is no proof that the responses he elicited all represented true hypersensitiveness to foreign protein. He also pointed out that allergic reactions may be due to the derivation of the catgut (sheep), its content of unremoved bacterial products, or to a histamine like substance it contains, alone, or in combination, and that they are especially observed after thyroidectomy. According to Kraussl et al,^{1381c} patients with a history of allergic disease and/or of previous operation were much more likely to react to intradermal tests with extracts of plain catgut, chromic catgut, or chromic acid than those without a history of either condition. Moreover, the incidence of wound disruption in animals previously sensitized by various methods to these substances was far greater than that in the control group. Pickrell and Clay,¹³⁸² however, were unable to sensitize animals with either plain or chromic gut

¹³⁷⁶ STERNBERG L. *J Allergy* 1: 83, 1929

¹³⁷⁷ LAHOZ C and RECATERO L. *Rev clin espan* 5: 361, 1942

¹³⁷⁸ JIMENEZ DIAZ C and SANCHEZ CUENCA B. *J Allergy* 6: 397, 1935

¹³⁷⁹ BENSON R L. *Arch Int Med* 64: 1306, 1939

¹³⁸⁰ SHANNON W R. *Minnesota Med* 26: 759, 1943

¹³⁸¹ HENRY M G. *Am J Surg* 54: 118, 1944

^{1381a} HINTON J W. *Arch Surg* 197: 209, 1936

^{1381b} BABCOCK W W. *Am J Surg* 27: 67, 1935

^{1381c} KRAUSSL C J, KESTEN B M and CIMIOTTI J G. *Surg Gynec & Obst* 66: 623, 1938

¹³⁸² PICKRELL A L and CLAY R C. *Surgery* 19: 333, 1944

CHAPTER XVI

CONTACTANTS

THE term contactants designates all those allergens that elicit manifestations of hypersensitiveness by means of direct contact with the skin or the mucosa. This group is probably the largest and the most heterogeneous of all allergens, embracing not only thousands of various chemicals, including cosmetics and drugs, but also innumerable plants and animal products that are capable of allergenic action. The clinical manifestations vary considerably. They include many types and degrees of inflammation of the skin and mucosa, such as dermatitis, urticaria, cheilitis, and occasionally stomatitis.

Until recently inflammation of the skin caused by contact with poison ivy or a cosmetic, for example, was known in America as "dermatitis venenata," while the European dermatologists used the term "eczema." But now that there is a far better understanding of the pathogenesis of this type of skin disease, the term "contact dermatitis" is almost universally employed. This term does not indicate, however, whether or not the contact dermatitis is of allergic character. In other words, it does not specify whether the condition is the result of local hypersensitiveness or of the capacity of the given substance to act as a primary irritant. Moreover, this differentiation cannot be made, as one might believe, on the basis of the history, clinical appearance, or histologic examination of the lesions, but only by means of properly performed skin tests.

When the condition is due to primary irritation, the patch test will elicit reactions (local inflammation) in nearly all persons tested. If there is an underlying allergy, on the other hand, the patch test will evoke a response only in the sensitive patient and not in normal controls. This difference is of the greatest importance, of course, for a number of reasons—therapeutic, prophylactic, and legal. The nomenclature should, therefore, be clear-cut in this respect.

Since this subject will later be discussed in detail (p. 692), only a few important points will be mentioned here. In this book the

terms "allergic contact dermatitis" and "toxic contact dermatitis" will be consistently employed. Naturally the term "toxic" is not employed in the narrow pharmacologic sense, but rather to designate strong local chemotoxic irritation. Special emphasis must be placed on the fact that the dermatitides contracted by industrial workers are by no means always allergic in nature. In fact, a large majority of occupational dermatoses are caused by primary chemical and physical irritation due to the use of alkalies, acids, oils, solvents, and dyes, which results, without underlying allergization, in clinical manifestations identical with those of allergic contact dermatitis.

Landsteiner⁴² and Sulzberger⁴ must be credited with the important contribution of recognizing the pathomechanism of allergic contact dermatitis and of its experimental reproduction. There can be no doubt that innumerable allergic occupational dermatitides have their origin in the combination of chemical substances that are in themselves nonantigenic (called haptens), with proteinogenous carriers, thus forming a complete allergen. This explains why so many chemical substances and physical agents may become etiologic factors in allergic contact dermatitis.

Landsteiner's haptization theory also explains how a primarily nonspecific irritation of the skin may prepare the way for a specific allergization. For example, if a housewife works with soft soap for a long time, she may readily acquire an ordinary toxic contact dermatitis. If, in this condition, she should be exposed to turpentine over a considerable period the hapten turpentine might combine with the skin protein that has been rendered foreign to the body as a result of the dermatitis, and thus form a conjugate protein antigen. The result is a complete antigen capable of producing a specific allergic turpentine dermatitis.

In the beginning, the lesions of contact dermatitis are fairly well localized to the site of the contact; subsequently, however, they

not infrequently spread and cover larger and often far removed areas. This progressive extension of the lesions goes on despite the fact that all contact with the agent has been suspended. The explanation may lie in an autosensitization to skin protein that has become foreign to the body.

It is likewise known to every physician that primary monovalent contact dermatitis may in time be rendered polyvalent specific and finally nonspecific. For example a dermatitis originally produced by bichloride of mercury (e.g. in the case of a nurse) may after a few weeks be produced by phenol and formalin as well and may be rekindled after a few months by exposure to any external noxa such as water soap friction or heat. A satisfactory explanation of this primarily specific and subsequently nonspecific broadened hypersensitiveness in allergic contact dermatitis is furnished by the concepts of metallergy (p. 28) and pathergy (p. 30).

It would be impossible to submit here a complete list of the agents that have been found to act as contactants or to enumerate the various trades and professions with respect to the dermatitis-producing substances peculiar to each. There is probably no organic or inorganic substance that cannot under appropriate circumstances become an allergic contactant. While some of the more important substances are mentioned in the following pages the reader seeking a more exhaustive treatment of the subject is referred to the textbooks on occupational diseases of the skin such as those of Schwartz and Tulipan¹⁷ and of Prosser White.¹⁸

The importance of an intimate knowledge of the causes of occupational diseases cannot be overestimated in our time for the present tendency is unquestionably toward increasing industrialization which in turn will naturally expose an ever growing number of workers in all ranks of life to the hazards of sensitization. The modern physician therefore requires in addition to his basic medical knowledge an understanding of technical working conditions and special knowledge of at least the principal hazardous exposures. Close cooperation of the industrial physician with plant chemists sanitary officers and technical

experts will often be necessary in solving the intricate problems presented by a given case. The Industrial Hygiene Division of the U. S. Public Health Service in Bethesda Md. has a special Dermatoses Section headed by Louis Schwartz. This section is in charge of work on all such problems and may be consulted in appropriate instances.

While no proper classification of contactants based on chemical grounds is as yet possible an attempt will be made to discuss them according to the nature of the active agent.

A. PLANTS AND THEIR PRODUCTS

Many plants irritate such a high percentage of human beings exposed to them that they may be classed as primary irritants. On the other hand some cases of plant contact dermatitis are from the beginning truly allergic in character. It may also be possible of course that the first effect was a toxic dermatitis and that the skin subsequently became specifically allergic to the plant by reason of the hapten mechanism. Differentiation can easily be made by the patch test method if the plant in question produces reactions in a high percentage of normal controls it must be considered as an irritant otherwise as an allergen.

There are many hundreds of plants that are capable of producing a state of hypersensitiveness. Only the most important representatives can be mentioned here. For further details and a complete bibliography the reader is referred to the excellent treatise by Touton¹⁹ and for a recent list of phanerogamous plants of dermatologic interest to Zwick.²⁰ Considerations of space also make it impossible to pay due attention here to certain questions of considerable practical importance—as for example just where in the respective plants the allergenically active substance is located. Thus in grasses parts other than the pollen may also produce allergic dermatitis in a given patient. On the other hand there are examples available to show that the allergen may be restricted to only one part of certain plants. For example Vryman

¹⁷ TOUTON K. Haute krankungen der haut phanerogamische Pflanzen. In Handb. d. Haut u. Geschlechtskr. vol. 4 pt. 1 1932.

¹⁸ ZWICK K. G. M. Bull. La. Cincinnati 8 60 194.

¹⁹ WHITE R. PROSSER. The Dermatologic Diseases. London 1934.

reported a case of vesicular dermatitis due to hypersensitiveness to dahlia; investigation revealed that the allergenic substance was found only in the marginal zone of the tuber. It must be remembered furthermore that the excitant effect not too infrequently varies with the time of the year because of a seasonal fluctuation in the intensity of the excitant.

Unfortunately, a methodical grouping of plants according to the principles of systematic botanic classification is not possible for the purpose of this discussion. However, it may be noted that the majority of offending plants belong to the following families: *Liliaceae*, *Ranunculaceae*, *Leguminosae*, *Euphorbiaceae*, *Umbelliferae*, *Ericaceae*, *Solanaceae*, *Compositae*, and *Urticaceae*. It would be ideal, of course, to subdivide the plants according to the chemical nature of their contained antigens. But we are not as yet in a position to do this. We shall, therefore, consider the more important plant contactants under the following headings: weeds, flowers, garden vegetables and fruits, and woods.

1. WEEDS

First and foremost among the weeds, mention must be made of rhus. Two types are responsible for the majority of the cases of the dreaded rhus dermatitis. *Rhus toxicodendron* (poison ivy and poison oak) in America and *R. vernicifera* in Japan and China. While Blank and Coca, Shelmire, and Stevens presented evidence to the effect that the excitants in poison ivy, poison oak, and poison sumac are allergenically and immunologically identical, the plants are by no means alike. Poison ivy (*R. toxicodendron radicans*) is either an erect bush, 2 to 4 feet high, a trailing shrub, or a climbing vine growing up on trees to heights of from one to several feet from the ground. The leaves have long stalks bearing three leaflets, are shiny on their upper surfaces, and at certain stages are red-tipped (Fig. 163). Poison oak (*R. toxicodendron diversiloba*) is generally a low shrub, 3 or 4 feet high, and occasionally, under special conditions, a treelike plant growing to a height of 14 feet, with leaflets somewhat resembling oak leaves (Fig. 164). Far less important is poison sumac (*R. toxicodendron vernix*), a member of the same family, which grows in swamps as a

shrub with slender stems and attains a height of 10 feet or more (Fig. 165). The American types of rhus cause inflammation of the skin in direct contact with the fresh sap of the plants; but it is the dried sap of the Japanese *R. vernicifera* on lacquered articles (mah jong pieces, earphones, and wooden ornaments such as bracelets and brooches)



FIG. 163 POISON IVY (*Rhus toxicodendron radicans*)
(Courtesy Bureau of Plant Industry, U. S. Department of Agriculture)

that is the cause of what is known as "lacquer dermatitis."

Regarding the question as to whether very hypersensitive individuals may develop skin manifestations from mere proximity to the plant, investigations have shown that this claim is erroneous, since the allergen is not volatile. It is true, of course, that the contact can be indirect, through ivy-contaminated intermediary objects, such as cloth-

ing shoes work tools door knobs heads of golf clubs steering wheels of automobiles pets udders of cows the hands of other persons who have touched poison ivy or even wind borne particles released when poison ivy is burned Howell³⁸⁶ confirmed this last type of exposure and concluded that the actual smoke of the burning plant is incapable of causing clinical dermatitis but that small

Shelmire³⁸⁴ repeatedly made the following experiment He gathered poison ivy thoroughly washed his hands with soap and water and then at intervals rubbed the skin of hypersensitive individuals He found that sufficient oleoresin to evoke dermatitis remained on his hands for as long as six hours These observations are readily understood in view of the fact that 0.0000015 cc. of urushiol (the chemical principle of *R. vernicifera*) in a drop of oil can produce a dermatitis when applied to the skin (Toyama)

Poison ivy allergy is unquestionably the most common disease of hypersensitivity in the United States Spain demonstrated the existence of this condition in 65 per cent of persons over 35 years of age and others have obtained comparable figures Boys and girls of camp age give a higher percentage of positive reactions than adults All the principle races appear to be equally susceptible provided opportunities for exposure exist Infants are not sensitive to poison ivy However by applying an ivy paste Straus was able to elicit cutaneous reactions in 13 per cent of the infants tested Rhus dermatitis is not followed by immunity On the contrary the degree of hypersensitivity appears to become higher No such thing as natural hypersensitivity to poison ivy has been observed in animals however it is possible to produce the condition experimentally employing guinea pigs and monkeys (see p. 45)

The active principle in poison ivy is called toxicodendrol in poison oak lobinol and in *R. vernicifera* urushiol All three appear to be identical they represent a catechol with an unsaturated side chain and the chemical behavior of a polyhydric phenol According to Shelmire³⁸⁷ the dermatitis producing principle is not an oil as previously thought but a dialyzable fraction of an oleoresin soluble in water

Two types of the dermatitis are observed First there is the toxic form which occurs in everyone shortly after adequate contact with the milky juice of the mature poison ivy plant The skin immediately turns white as though it had been painted with trichloroacetic acid after a brief interval the area becomes black



FIG. 164. POISON OAK (*Rhus diversiloba*)

(Courtesy Bureau of Plant Industry U. S. Department of Agriculture)

particles of the leaves soot and charred matter carried by the smoke may contain sufficient active principle to do so A unique instance is that of a rhus sensitive veterinarian who had a severe dermatitis on the arms after performing a rectal examination on a cow which had eaten poison ivy leaves (Urbach)

because of the oxidation of the ivy juice. An eschar forms and then sloughs off in from eight to ten days. Complete healing with scar formation requires about two weeks. This juice has the same caustic effect on the skin of all animals tested (Shelmire).

In contrast to this toxic dermatitis, there is the allergic dermatitis that can be elicited in human beings and certain species of animals ten days after experimental exposure (Field and Sulzberger¹²⁵³), or that develops in hyper-

acute dermatitis in the spring or early summer and continues until the first killing frost. At the onset, the eruption is usually erythematous, scaling, and pruritic. During the first few years the dermatitis is strictly seasonal, corresponding closely with the growing season of the plant, with frequent exacerbations caused by massive exposures. Sooner or later the eruption becomes perennial; the erythema, edema, oozing, and crusting disappear, but the pruritic, lichenified areas



FIG. 165 POISON SUMAC (*Rhus toxicodendron vernix*)

(Courtesy Bureau of Plant Industry, U. S. Department of Agriculture)

sensitive individuals a few hours after contact, usually running a stormy course of one to three weeks or longer. Its clinical manifestations may be acute or chronic. The former type generally includes dermatitides with marked swelling and vesiculation (FIGS 166, 167), less commonly erysipelas-like erythema, accompanied by high fever and prostration. Rarely, visual disturbances, delirium, and even death have been observed.

The chronic eruption usually begins as an

persist even during the winter months, while severe acute flares are observed during the growing season of the ivy plants. Moreover, not only the skin, but also the mucosa of the mouth and gastro-intestinal tract may become inflamed—for example, after ivy leaves have been chewed, or after a tincture of ivy has been taken internally.

The diagnosis is generally easy. Most patients are aware that they have been in contact with poison ivy or poison oak a day or two before. The manifestations are usually confined—in the beginning, at least—to the

¹²⁵³ FIELD, H., and SULZBERGER, M. B. *J. Allergy* 7: 139, 1936

areas of the body that have been exposed to the plant. However, lesions are not infrequently observed on the genitalia and about the eyes and mouth—the active principle being transferred by the hands. In this connection, Pratt and Corson¹³³³ found that, contrary to popular opinion, the fluid contents of naturally acquired and patch test induced poison ivy vesicles and bullae do not produce

the patient will acquire a poison ivy dermatitis under ordinary conditions of exposure (Keil¹³³⁹). A negative patch test properly performed rules out the possibility of poison ivy as the cause. The test is done by applying to the skin a minute portion of a bruised fresh leaf or a particle of dried poison ivy seed of the size of a grain of sand. Care must be taken however not to leave the patches on the

ATYPICAL LOCALIZATION OF POISON IVY DERMATITIS



FIG 166 Very severe acute dermatitis of face



FIG 167 Lesions confined to feet; patient wore open sandals

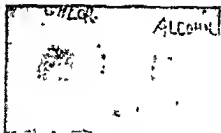


FIG 168 POISON IVY PATCH TESTS WITH CHLOROFORM AND ALCOHOL EXTRACTS

Showing that active principle is probably an oleoresin

new lesions on the same individuals or on other susceptible persons.

In cases in which the diagnosis seems doubtful, it can be determined by a patch test (FIG 168). It should always be remembered, however, that a positive test does not prove that the dermatitis is due to poison ivy, but simply indicates sensitization, past or present. Moreover, it does not necessarily mean that

skin longer than one hour for nonspecific positive reactions are not unlikely to appear after prolonged exposure. Patch tests with acetone extracts of the leaves are more accurate. This method may incidentally be used in relation to all plant dermatitides.

TECHNIC. One part by weight of the leaves or some other portion of the plant such as the seeds is extracted for twenty-four hours with five parts of acetone with frequent shaking. The acetone extract is then evaporated down to one-fourth the original volume and stored in tightly stoppered bottles properly labeled and dated. The stoppers are fitted with a glass rod for convenient application in testing. The patient should be advised to remove the patch test immediately and wash the site with soap and water if untoward reactions ensue. The specific oleoresins of the various plants can also be used for patch tests.

The management of plant dermatitis may be divided into prophylaxis and treatment. The prophylactic measures include (1) avoidance or eradication of the noxious weeds, (2) protection of the skin, and (3) specific

immunologic methods. The therapeutic measures comprise local applications and specific hyposensitization.

If avoidance of poison ivy in a given locality is impossible, the patient should endeavor to eradicate the weeds. L. W. Kephart of the Bureau of Plant Industry of the United States Department of Agriculture has issued a very valuable bulletin on the control of poison ivy.

Many local prophylactic methods have been advocated for the purpose of oxidizing—and thus rendering nonirritant—the active principle of the plant. Schwartz et al.¹²⁹¹ recommended the use of an ointment containing sodium perborate as a nonirritant and non-staining oxidizing agent.

The ointment contains 10 per cent sodium perborate in a base consisting of the following: castor oil 21.5 per cent, olive oil 21.5, anhydrous lanolin 21.5, dighcol stearate 12.9, refined paraffin 8.6, boric acid 2.0, and Duponol WA pure 2.0. A thick layer of the ointment is applied before possible exposure. Clothes must be removed before the ointment is washed off to prevent exposure of unprotected skin to contaminated clothes. Before clothes are again worn, they must be decontaminated.

Potassium permanganate (1:1,000) and ferric chloride (3 to 5 per cent, in equal parts of glycerin and water) are also advocated for prophylaxis, but great care must be exercised in the use of these remedies, since they sometimes leave unsightly stains or even persistent pigmentation of the skin.

Howell,¹²⁹² however, holds that no known topical prophylactic application, including thorough and prolonged washing with soap and water, 10 per cent ferric chloride in solution or ointment, 10 per cent potassium permanganate, and sodium perborate ointment, is capable of preventing poison ivy dermatitis or mitigating the eruption after contact has occurred. Petrolatum and ointment bases containing oils caused spread of the dermatitis, due to the solubility of the ivy oleoresin in oily mediums.

Since oxidation destroys the eczematogenic properties of poison ivy, Sizer and Prokesch¹²⁹³ recently employed mushroom tyrosinase as a means of enzymatic detoxication, and found

that applied before or simultaneously with the poison ivy concentrate it greatly reduced the dermatitis-producing capacity of the latter. If it is equally successful when applied some time after the toxicant has reached the skin or, preferably, after erythema has developed, a new method of treating poison ivy dermatitis will be available.

The local treatment of the typical active case consists chiefly in the application of soothing and antipruritic lotions. A formula is as follows:

	Gm or Cc	
Rj Phenol	1	gr. xv
Zinc oxide		
Talc	\overline{aa} 20	\overline{aa} 5 v
Glycerin		
Water	\overline{aa} q s ad 100	\overline{aa} q s ad f3 iii

M Sig: Apply locally often enough to stop itching

Where it is desired not to use phenol, 2 per cent calmitol may be substituted in this prescription. In cases where the lesions become secondarily infected, a 5 per cent sulfathiazole cream or penicillin ointment may be used. Cold compresses of 3 per cent boric acid or 1:5,000 potassium permanganate are beneficial during the acute stages. Wet dressings with aluminum acetate are exceedingly helpful.

The solution is prepared by dissolving one level teaspoonful of lead acetate in one third glass of boiling water, and three level teaspoonfuls of alum in one-third glass of boiling water. The latter is poured into the former, the white precipitate allowed to settle, and the clear solution poured into a bottle and appropriately labeled. It is then used as a wet dressing for not more than ten minutes, although if itching recurs a little more may be dabbed on and permitted to dry. In new cases a single application is often all that is necessary.

Epstein¹²⁹⁴ reported one or two injections of calcium intravenously to be helpful in reducing the inflammation and pruritus, calcium therapy being continued thereafter by mouth.

Specific treatment is employed both for prophylaxis, either preseasonal or perennial, and for active or coseasonal therapy. There are two principal methods—the parenteral and the oral administration of poison ivy extracts or their oleoresins. It was Strickler¹²⁹⁵ who first reported favorable results in

¹²⁹¹ SCHWARTZ, L. DUNN, J. E., and GOLDMAN, F. H. Pub. Health Rep. 57: 578, 1942

¹²⁹² HOWELL, J. B. Arch. Dermat. & Syph. 45: 313, 1943

¹²⁹³ SIZER, I. W., and PROKESCH, C. E. Science 101: 517, 1945.

¹²⁹⁴ EPSTEIN, S. Letters, Internat. Corr. Club of Allergy, Series 8: 4, 1944

¹²⁹⁵ STRICKLER, A. J. Cutan. Dis. 36: 327, 1918, J. A. M. A. 80: 1588, 1923

rhus dermatitis from specific treatment administered intramuscularly. While the effectiveness of this method for phylactic therapy as well as for preseasonal protection has been confirmed by many investigators (Spain and Cook, Blank and Coca, Caulfield, Mollitsch and Poliakoff, and others), certain investigators (Krause and Weidmann, Corson, Zisserman and Birch, Greenberg and Mallozi, and others) were unable to corroborate it. The present writers have only occasionally observed successful prophylaxis by this method. It has, however, shortened the course of the disease in some acute cases. On the other hand, severe exacerbations have been seen by Pillsbury,¹³⁹⁵ Stevens,⁶⁷⁷ and the present writers. The reason for these divergent results is not known.

French and Halpin¹³⁹⁷ reported the use of a 5 per cent extract of poison ivy in absolute alcohol in the treatment of 2,544 cases of dermatitis. Just prior to injection the concentrated extract is diluted 1:10 with saline, and administered intramuscularly in slowly increasing amounts daily for four or five days, reaching a dose of 0.4 or 0.5 cc. of the 1:10 dilution. Results were satisfactory in the majority of patients, particularly as regards control of itching and shortening the course of hospital treatment. Experience with prophylactic use of this extract was less extensive, but appeared to be promising. The junior author has found this method of distinct value in the therapy of a number of cases. Strauss and Spain^{1397a} recently described a method for preparing a new type of extract from poison ivy and like plants (as well as pollen oils) whereby the active principle consists of an alum precipitated pyridine ivy complex suspended in saline solution. This was found capable of producing poison ivy sensitization of guinea pigs by the parenteral route, and gave encouraging clinical results when employed phylactically and prophylactically.

A comprehensive review article on the status of poison ivy extracts was recently presented by Stevens.⁶⁷⁷

The second and increasingly popular method of specific hyposensitization is the oral one, which, incidentally, is well over a hundred

years old. In 1829, Dakin reported on the beneficial effects of chewing the leaves of the poison ivy plant, adding that it was an old practice among the American Indians. In 1898, Alumbaugh made an alcoholic extract and claimed good results with a third decimal dilution taken hourly for twenty-four to forty-eight hours. Twenty-five years ago Strickler, also Schamberg, recommended prophylactic administration of 2 drops of tincture of *Rhus toxicodendron* to be increased by 1 drop at each dose, and taken in water three times daily. This method did not, however, come up to expectations, in fact, pruritus, anal dermatitis, and certain gastro-intestinal disturbances were often observed. Gold and Masucci¹³⁹⁸ recently reported successful prophylaxis with an oral extract of the leaf in graduated doses, but state that nearly all the patients develop erythema, vesicular dermatitis, or pruritus. Ellis¹³⁹⁹ obtained good prophylactic results employing oral administration of poison ivy antigen in tablet form.

Within the past few years, Shelmire,⁷⁸⁷ who has made especially valuable contributions to the study of weed allergy, has recommended a new prophylactic method, consisting of oral administration of specific oleoresins, with which he himself as well as Goldman⁷⁸⁸ had excellent results.

TECHNIC. One drop of a 1:25 dilution of ivy oleo-resin in corn oil is given daily for one week, 2 drops daily the second week, 5 drops the third week, 10 drops the fourth week, and thereafter 15 drops every other day until the contents of a 1 ounce bottle have been consumed. If a covered patch test with a 1:100 dilution of ivy oleoresin in corn oil is positive at this time, oral treatment should be continued. Should intolerance for the oleoresins develop, as evidenced by a flare up of healed patch sites or the appearance of erythema, urticaria, flushing, or abdominal cramps, treatment should be interrupted and resumed later with a lower dilution. To prevent dermatitis of the lips and allergic reactions of the mouth and throat, the drops are given in an ordinary gelatin capsule or taken well diluted in cream, through a straw.

It is known that the leaves of poison ivy plants differ considerably in "toxic" potency, depending on whether or not they are dried out, dry leaves losing most of their allergenic

¹³⁹⁵ PILLSBURY, D. M. personal communication.

¹³⁹⁷ FRENCH, S. W. and HALPIN, L. J. *Ann. Allergy* 1: 331, 1943.

^{1397a} STRAUSS, M. B. and SPAIN, W. C. *J. Allergy* 17: 1, 1946.

¹³⁹⁸ GOLD, H. and MASUCCI, P. *ibid.* 13: 157, 1942.

¹³⁹⁹ ELLIS, F. A. *ibid.* 14: 537, 1943.

capacity. On the other hand, the senior author found that dried poison ivy seeds have a uniform potency, a distinct advantage in oral therapy. The best results are afforded by the perennial technic. Children under 10 years of age receive 1 mg. in enteric coated tablets (Rhu-Sem*) three times a week, the dose being increased to 1 tablet a day from March to the first frost. For adults the same schedule is followed with tablets each containing 5 mg. The senior author has used the dried poison ivy seeds for both prophylaxis and treatment for the last three years. About 50 highly allergic patients who took Rhu-Sem perennially remained entirely free despite considerable exposure to poison ivy. If a dermatitis develops in an unprotected individual, it is often possible to mitigate the course of the condition by giving one capsule daily on an empty stomach.

Far less commonly, short and giant ragweed, parthenium, cocklebur, burweed, bitterweed, sneezeweed, firewheel, marsh elder, alfalfa, bur clover, eugenia bush, and other weeds are the cause of severe dermatitis in farmers and others whose work or recreation take them out of doors. In Australia, the capeweed has been similarly reported. The unclothed parts of the body are, of course, most frequently affected, later, however, other areas as well become involved through contamination with the allergen. While the manifestations generally appear only during the growing season of the given plant, the eruption may occasionally be perennial. This is explained by the fact that the patient may be constantly exposed to the effect of the weeds through dust particles remaining in his clothes, or by working in barns or warehouses holding traces of the causative plant (Brunsting and Anderson¹⁴⁰¹). Likewise, Shelmire¹⁴⁰² has demonstrated that some cases of so-called "milker's eczema" were due to weed oleoresins with which the cow hair was contaminated. Of the weeds, the marsh elders, including narrow leaf marsh elder (*Iva angustifolia*), as well as burweed marsh elder (*Iva xanthifolia*) and small poverty weed (*Iva axillaris*) appear to

be common offenders (Smith, Prince, and Cole¹⁴⁰³; Bowen).

It is erroneous to consider these usually seasonal dermatoses routinely as pollen dermatitides. While ripe unwashed pollens give strongly positive reactions on patch testing, other parts of the plants, such as the leaves, stalk (Coca), and seeds (Urbach), can also do so. According to Brown, Milford, and Coca,¹⁴⁰² the plant oils are the active principle in the production of certain eczematous pollen reactions of the contact type. In a series of exhaustive studies, Shelmire¹⁴⁰⁴ showed that the pollen of every weed contains an ether-soluble oleoresinous dermatitis-producing fraction and a water-soluble albuminous hay-fever-producing fraction. These specific oleoresins are present not only in the pollen, but also in other parts of the plants. This is not to say, however, that every weed dermatitis is necessarily attributable to the oil fraction. Thus, Chobot reported that an extensive dermatitis was provoked in a hay fever patient by patch testing with the purified albumin precipitate of the pollen. Contact dermatitis from ragweed pollen is a common occupational hazard of workers in the flour and grain industries (Jordon, Campbell, and Osborne¹⁴⁰⁵). Contact dermatitis due to airborne pollens is discussed further in chapter XXI.

The diagnosis of contact dermatitis due to weeds can be confirmed by patch tests with ether or acetone extracts of the plants. Hypo-sensitization can be accomplished by oral administration of oleoresin in oil, as in rhus dermatitis.

Saunders¹⁴⁰⁶ has pointed out that mites of the family *Tyroglyphidae* in straw can cause eruptions indistinguishable from contact dermatitis. A similar warning is pertinent more generally with reference to "pseudophytophagous" dermatitides produced by various insects whose habitats are the plants of the garden and field (Zwick¹⁴⁰⁷), as well as mites, particularly the *Pediculoides ventricosus* which causes "grain itch," and molds infesting

¹⁴⁰¹ SMITH, W. A., PRINCE, H. E., and COLE, M. L. *J. Allergy* 13: 371, 1912

¹⁴⁰² BROWN, A., MILFORD, E. L., and COCA, A. F. *ibid.* 2, 301, 1911.

¹⁴⁰³ JORDON, J. W., CAMPBELL, P. C., and OSBORNE, E. D. *Arch. Dermat. & Syph.* 46: 721, 1942.

¹⁴⁰⁴ SAUNDERS, T. S. *ibid.* 50: 245, 1944.

* Manufactured by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa.

¹⁴⁰⁵ BRUNSTING, L. A., and ANDERSON, C. R. *J. A. M. A.* 113: 1285, 1934.

vegetation. Only diagnostic care and appropriate tests will distinguish these cases from those due to epidermal sensitization to the plant itself.

Although poisonous rhus species are confined to North America, eastern Asia, and Japan, Mernit¹⁴⁰⁸ has pointed out that various tropical representatives of the family *Anacardiaceae*, to which poison ivy belongs, are capable of causing violent dermatitis similar in many respects to poison ivy dermatitis. They occur as woody plants, chiefly trees, but including some shrubs and vines and are found almost everywhere in the Indo Malay sian, Micronesian, and western Polynesian regions. Eruptions follow contact with the fresh sap, which quickly turns black on exposure to the air, with fresh leaves, or in certain species with freshly sawed lumber. The mango like trees are particular offenders. Their active principle is the same as that of rhus. Among the interesting clinical examples may be mentioned the report of Livingood, Rogers, and Fitz Hugh¹⁴⁰⁹ that soldiers suffered dermatitis from wearing clothes marked by native dhobies or washermen with the black indelible liquid content of the nut of the rai or bella gutti tree, probably *Semecarpus ana cardium*, they suggest that the term "dhobie itch" as referring to tinea cruris and epidermophytosis be discontinued. Goldsmith¹⁴⁰⁷ observed 16 cases of acute dermatitis from contact with a mail pouch contaminated with bilhawanol oil or marking nut oil (*Ana cardium occidentale*). The manzanillo tree in the Caribbean area has been responsible for numerous cases of severe dermatitis venenata (Satulsky and Wirts¹⁴⁰⁸) and severe kerato conjunctivitis (Snow and Harley¹⁴⁰⁹). Contact may occur not only with the tree itself, but even with the wet sand around it or with dew falling from the tree. Hitch¹⁴¹⁰ observed dermatitis from contact with the acayou tree (*Semecarpus atra*) in New Caledonia, the

Loyalty Islands, and the New Hebrides group. Markson¹⁴¹¹ reported 8 cases of dermatitis of exposed parts in candy factory workers caused by the Brazil nut and its oil. Patients sensitive to poison ivy invariably also react to cashew nut shell liquid, one of the products of the *Anacardiaceae* family of plants (Keil Wasserman and Dawson¹⁴¹²). This substance is used in the manufacture of certain resins and plastics which are incorporated in brake linings and electrical insulating materials. The dermatitis arises from handling the raw oil, and in some cases even the finished resinous products derived from it.

2 FLOWERS

Hypersensitiveness to *primrose* occupies approximately the same position in Europe as does rhus allergy in America. Primrose is a very common house plant in Europe. The hypersensitiveness is particularly in relation to the Japanese primrose (*Primula obconica*). The active principle is primin with which Bloch¹⁴⁰⁷ succeeded in allergizing 100 per cent of the human beings and animals tested. Perutz and Rosner¹⁴¹¹ as well as Urbach¹⁴¹² were able to transfer primrose dermatitis passively. The latter was repeatedly able to reproduce the clinical picture of dermatitis by the passive transfer method, using fluid from spontaneously formed blisters (p. 151). This unequivocally proves the allergic nature of primrose dermatitis. Itching, erythema, papules, and bullae are the chief manifestations, generally confined to the sites of contact. Not infrequently, however, all of the skin becomes allergized and even the mucosa of the eyes and mouth (Bircher) may become involved.

Palmer and Freeman¹⁴¹⁴ reported erythema of the face and follicular eruptions as well as extensive dermatitis on the hands and forearms—the so called lily rash—in persons engaged in reaping and mowing fields of narcissus. These patients presented positive immediate reactions to the pollen and delayed reactions to the leaves and stems of the narcissus plant. These authors achieved almost

¹⁴⁰⁶ MERRILL E. D. J. A. M. A. 124: 222, 1944. Bull. U. S. Army M. Dept. No. 87, p. 115, April 1945.

¹⁴⁰⁸ LIVINGOOD C. S., ROGERS A. M. and FITZ HUGH T. J. J. A. M. A. 123: 23, 1943.

¹⁴⁰⁷ GOLDSMITH N. R. ibid. 123: 27, 1943.

¹⁴⁰⁸ SATULSKY E. M. and WIRTS C. A. Arch. Dermat. & Syph. 47: 797, 1943.

¹⁴⁰⁹ SNOW J. S. and HARLEY R. D. ibid. 49: 236, 1944. HARLEY R. D. Am. J. Ophth. 27: 628, 1944.

¹⁴¹⁰ HITCH J. M. U. S. Naval M. Bull. 42: 1111, 1944.

¹⁴¹¹ MARKSON I. S. Arch. Dermat. & Syph. 46: 831, 1942.

¹⁴¹² KEIL H., WASSERMAN D. and DAWSON C. R. Science 102: 279, 1945.

¹⁴¹³ URBACH E. Dermat. Ztschr. 69: 245, 1933.

¹⁴¹⁴ PALMER W. H. and FREEMAN J. Lancet 2: 750, 1934.

total desensitization by prophylactic injections of leaf or stem extract.

In addition, the following flowers are reported to have produced dermatitis: aster, camomile, carnation, clove, cosmos, chrysanthemum, daffodil, daisy, flax, gaillardia, helenium, hop, hyacinth, iris, marigold, mistletoe, petunia, philodendron, pyrethrum, tulip, verberna, and zinnia. Florists and housewives are most often affected. The hands, forearms, face, and neck usually show a recurrent vesicular eruption. Sometimes, though rarely, contact urticaria may result (Shelmire⁷⁵⁷).

In Hawaii, common causes of dermatitis are the kahlu or rain flower (*Grevillea banksii*) and the mango tree, both the fruit and the leaves of the latter causing eruptions.

Now and again the allergen is contained only in the bulbs or the roots. Thus, Bertwistle¹¹³ and Caulfield¹¹⁸ reported dermatitis due to tulip bulbs, Johnson¹¹⁷ a case due to hyacinth bulbs and Derbes¹¹⁵ one due to narcissus bulbs. Rappaport and Welker¹¹⁹ found that the active substance was confined to the ether-soluble fraction of the plant.

Orris root is the dried root of certain species of the iris (see p. 278). While it acts chiefly as an inhalant allergen, the literature contains quite a few cases of dermatitis, particularly of the face, due to orris root. Dermatitis due to *derris root* was described by Dorne and Friedman,¹²⁰ and to the related *Lonchocarpus* or timbó by Oliveira Lima.⁹⁷²

Some plants, such as wild parsnip (*Pastinaca sativa*), cow parsnip (*Heracleum*), common fig (*Ficus*), common agrimony (*Agrimonia eupatoria*) and herb of grace (*Ruta graveolens*), are photosensitizers. They produce a very characteristic dermatosis known as "meadow grass dermatitis" (dermatitis bullosa striata pratensis). The clinical picture of this condition, first described by Oppenheim and Fessler,¹²¹ consists in bright-red, slightly elevated spots, and narrow, rather long streaks that are intercrossed here and there. Vesicles with watery content are seen on top of these red spots and

streaks (Fig 169). The characteristic history is that the patient was sitting or lying on a grassy field on the previous day, while more or less disrobed, and it will often be seen that the skin condition is confined strictly to those areas that came into direct contact with the grass. Accompanied by intense itching, the dermatosis makes its appearance some twenty-four hours after the exposure. The condition subsequently assumes a streaky striped appearance, looking at first glance as if the skin might have been scratched by a sharp-edged instrument. The condition heals rapidly, leaving residual pigmentation, however, that persists for a long time. The first such case in the



FIG. 169. MEADOW GRASS DERMATITIS

American literature is the one reported by Corson.¹²²

Kitchevatz¹²³ set up the hypothesis that the disease may be caused by the photodynamic action of some of the components of the plants. He pointed out that when a person with wet skin—after bathing, for example—lies down on the grass, the weight of his body, or possibly some other trauma, crushes the plant and thus expresses the active substance, which in turn impregnates the skin; this would ex-

¹¹³ BERTWISTLE, A. P. Brit. M. J. 2, 255, 1935.

¹¹⁸ CAULFIELD, A. H. W. J. Allergy 8: 181, 1937.

¹¹⁷ JOHNSON, D. W. Arch. Dermat. & Syph. 32, 239, 1935.

¹¹⁵ DERBES, V. J. Southern M. J. 35, 912, 1942.

¹¹⁹ RAPPAPORT, B. Z., and WELKER, W. H. J. Allergy 8, 379, 1937.

¹²⁰ DORNE, M., and FRIEDMAN, T. B. J. A. M. A. 115, 1269, 1940.

¹²¹ OPPENHEIM, M., and FESSLER, A. Dermat. Wchnschr. 86: 183, 1928; Dermat. Ztschr. 55: 191, 1929.

¹²² CORSON, E. F. Arch. Dermat. & Syph. 32: 616, 1935.

¹²³ KITCHEVATZ, M. Bull. Soc. franc. de dermat. et syph. 40: 761, 764, 1933.

plain why only these areas react to light Hirschberger and Fuchs, indeed, were able to reproduce the characteristic features of dermatitis pratensis by rubbing the skin with elements of parsnip and then exposing the treated areas to sunlight. According to the experimental work of Kuske the active photosensitizer involved belongs to the furocumarin group. Pursuing his investigations with certain chemical representatives of this group of substances, including bergapten from oil of bergamot and oxypencedamin from the roots of *Pencedamum ostruthum*, Kuske regularly succeeded in producing skin responses after exposure to ultraviolet light. By means of various filters and sources of light, the active spectral range was found by Jensen and Hansen¹²⁴ to be located in the long-wave section of the ultraviolet band of the spectrum.

3 GARDEN VEGETABLES AND FRUIT

Skin eruptions have been observed, mainly in housewives, grocery clerks, canning factory workers, and truck gardeners, as due to the following vegetables and fruits: angelica, artichoke, asparagus, carrots, celery, cinnamon, corn, figs, garlic, grapes, grapefruit, Irish potatoes, lemon lime, mint, mustard, orange, parsnip, potato, radish, spinach, tomato, turnip greens, vanilla, and water cress. Occupational dermatitis in the food industry has been reviewed by Schwartz.¹²⁵ In highly sensitive children, circumoral dermatitis not infrequently follows the eating of certain foods, particularly spinach, carrots, tomato juice, or orange juice. While in the majority of cases the skin eruption takes the form of an acute or chronic dermatitis, general urticaria has occasionally been reported. Thus Vaughan²¹ observed a woman in whom this disease could be traced to work with starched sheets, after the use of cornstarch was abandoned, the urticaria promptly cleared up. There are also some reports of cheilitis due, for example, to cinnamon oil in chewing gum (Miller⁷¹⁴).

Furthermore, dermatitides due to *asparagus* have quite frequently been seen in workers in asparagus canning plants (Sternthal). The senior author observed the case of a vegetable cook who worked in the kitchen of a big hotel

after handling a large quantity of asparagus, the patient presented a diffuse weeping dermatitis on the left hand (Fig. 170), the area that had been in contact with the asparagus juice, the allergic nature of the condition was confirmed by a positive reaction to asparagus. Since the patient stated that whenever she ate asparagus she suffered itching of the gums and observed small vesicles on the mucosa of the gums, an epimucous test was made by pressing the stem of an asparagus stalk against the mucosa of the gums for one hour definite local vesicle formation was observed.

Carrots have also been found to contain a skin sensitizing principle capable of producing allergic dermatitis in workers industrially exposed to their juice (Peck, Spolyar, and Mason¹²⁶).



FIG. 170 DERMATITIS DUE TO ASPARAGUS

Confined to left hand in which patient held stalks while cleaning them.

Henry¹²⁷ found that of 391 workers engaged in washing celery hearts, 30 per cent were affected with contact dermatitis. The causative agent is the limonene contained in the celery oil and liberated during the washing process. Similar conditions are observed in the Orient. Thus Behdjiet¹²⁸ reported fig dermatitis as a common occupational disease. The juice of the raw figs, squeezed out onto the hands when the figs are picked, very frequently causes bullous inflammation, while the milky sap of the stem of the fig can cause a photosensitization dermatitis. Hadley¹²⁹ made the interesting observation on himself that not only did

¹²⁶ PECK S M, SPOLYAR L W and MASON H S Arch Dermat & Syph 49 266 1944

¹²⁷ HENRY S A Brit J Dermat 50 342 1938

¹²⁸ BEHDJET H Bull Soc franc de dermat et syph 40 787 1933

¹²⁹ HADLEY F B personal communication

¹²⁴ JENSEN T and HANSEN K G Arch Dermat & Syph 40 566 1939

¹²⁵ SCHWARTZ L Indust Med 13 899 1944

contact with the juice of the foliage of wild *parsnips* promptly result in a vesicular dermatitis, but also that the ingestion of cooked cultivated parsnips induced urticaria.

Finally, workers engaged in sorting and peeling oranges and lemons not infrequently present eczematous eruptions on the hands and arms, as well as on the face. The senior author¹⁰⁹ determined that the causal factor in these cases is the volatile oil contained in the outer layers of the peel. However, in patch testing with citrus peel, special care must be taken to avoid breaking of the cells in the peel and consequent exposure of the skin to the citrus oils, which are primary skin irritants (Schwartz¹²⁰). Hazen¹²¹ found orange skin to be a not infrequent cause of dermatitis of the eyelids in housewives and others. By patch and elimination tests he showed that in some cases the response was confined to the skin of Florida oranges and did not occur with that of California oranges. An excellent summary of citrus fruit dermatitis was contributed by Beerman, Fonde, and Callaway.¹²²

In connection with the subject of hypersensitiveness to garden vegetables, allergy to the tobacco plant must not be overlooked. We must consider here, of course, all the various dermatitides observed in cigar makers and in tobacco workers and dealers. In some instances, according to Vero and Genovese,¹²³ the allergen is to be found not in the untreated tobacco leaves, but in leaves that have undergone curing and fermentation processes. In still other cases, the hypersensitiveness is in relation to gum arabic, gum tragacanth, or glucose syrup, which are used for preparing the wrappers in cheap cigars. Cigar and cigarette smokers may acquire cheilitis or circumoral or finger dermatitis through the action of certain added ingredients (e.g., diethylene glycol—Newman¹²⁴), or may become hypersensitive to the paper of the mouthpiece (Lenk¹²⁵). Occasionally, urticaria (Rappaport and Hoffman¹²⁶) or angioneurotic edema (Vaughan²⁷) is observed. The acrolein combustion prod-

ucts of the glycerin in cigarettes were found to be the cause of the urticarial responses reported.

4. Woods

A glance at the extensive literature on wood allergy will certainly suffice to create the impression that every wood can, under appropriate conditions, produce allergization. Exotic trees are especially frequent causes of dermatitis. Senebar,¹²⁸ who has contributed a valuable review of this subject, has listed the following as the most important: aroeira, Borneo rosewood, boxwood, Brazilian walnut, cocobolo, coco wood, ebony, eucalyptus, Japanese hardwood, lemonwood, macassar wood, mahogany, mahwah, mango wood, olive-wood, partridge wood, redwood, rosewood, satinwood, teakwood, and yew. It must be mentioned, however, that native woods act as allergens far more frequently than is commonly supposed. Outstanding among them are acacia, alder, beech, birch, chestnut, cedar, elm, maple, mesquite, oak, pine, poplar, prune, and spruce. On the other hand, there is a marked variation in the frequency with which the different woods produce symptoms.

The fact that wood may contain a primary irritant of non-allergic nature is illustrated by Landor's¹²⁷ report of an epidemic outbreak of dermatitis in Singapore due to the smoke of Binjai wood (the bark of *Mangifera caesia*, commonly known as the wild mango) when burned in kitchen stoves. The irritant was shown to be volatile.

Needless to say, the allergic character of a dermatitis must always be confirmed by appropriate skin tests, using moist sawdust and alcoholic or etheric extracts of the woods (Fig. 171), for it must be remembered that nonallergic inflammation can quite readily be produced by the nonsaturated resinous acids or alkaloids. It is also essential to perform these tests in order to determine whether the allergen is contained in the bark, the freshly cut wood, dried wood, sawdust, leaves, or other parts of the tree. Woodcutters, sawmill workers, charcoal burners, hunters, cabinet-makers, and joiners seem to be especially ex-

¹⁰⁹ SCHWARTZ, L. Skin Hazards in American Industry, pt. 3. Pub. Health Bull. 249, 1939.

¹²¹ HAZEN, H. H. Arch. Dermat. & Syph. 49: 253, 1944.

¹²² BEERMAN, H., FONDE, G. H., and CALLAWAY, J. L. ibid. 38: 225, 1938.

¹²³ VERO, F., and GENOVESE, S. ibid. 43: 237, 1941.

¹²⁴ NEWMAN, B. A. J. A. M. A. 111: 25, 1938.

¹²⁵ LENK, Dermat. Wchnschr. 104: 614, 1937.

¹²⁸ SENEAR, F. E. J. A. M. A. 101: 1527, 1933.

¹²⁷ LANDOR, J. V. Brit. J. Dermat. 55: 17, 1943.

posed to allergization. The injurious factor often appears to be volatile in nature (etheral oils)—a view supported by the fact that the manifestations can be seen in a hypersensitive individual as soon as he enters a carpenter's shop or any place where woodcutting is going on. In some instances the hypersensitivity is not to the natural wood but to the fungi or mites living as parasites in the wood. It is important to remember furthermore that there is such a thing as hypersensitivity to the finished wood in everyday objects—e.g. handles of knives, canes or bowling balls of cocobolo wood (Abramowitz and Swartz⁴²⁸). Of course allergy to stains, varnishes, lacquers and other finishes must be excluded.



FIG 171 POSITIVE PATCH TEST REACTION TO MOIST SAWDUST OF BEECHWOOD

The eruptions caused are of various types the most common being acute dermatitis (FIG 172) which occasionally assumes an erysipelas-like appearance. The exposed areas are of course affected first but involvement of the genitalia and even of the entire body is not infrequently observed. Perspiration and oily skin are predisposing factors. Finally the mucous membranes, particularly those of the respiratory system and the conjunctiva may be affected.

B ANIMAL PRODUCTS

Although far less commonly than plant products or chemical agents, animal sub-

stances can also produce contact dermatides or contact urticaria. *Sheep's wool* and *silk* are the outstanding representatives. While the literature contains relatively few references to these substances as contactants (Taub⁴²⁹ Hill⁴³⁰ Lord⁴⁴⁰ Moll⁴⁴¹ and others) the writers' own observations have led them to believe that both sheep's wool and silk not infrequently act as allergens, particularly as the cause of dermatitis of the neck, the chest



FIG 172 ALLERGIC DERMATITIS IN LUMBERMAN DUE TO HYPERSENSITIVENESS TO BEECH

(FIG 173) the arms and the hands (FIG 174) in adults as well as of the face in infants. This is confirmed by the observation of Davies and Barker⁴⁴² that 16.4 per cent of the admissions to the skin wards of a large military hospital were the result of dermatoses proved to be wholly or partly due to intolerance of the skin to contact with woolen textiles (khaki uni-

⁴²⁸ HILL L W J Pediatr 16:6, 1940

⁴²⁹ LORD L W Arch Dermat & Syph 26:707, 1932

⁴⁴⁰ DAVIES J H T and BARKER A N Brit J Dermat 56:33, 1954

⁴⁴¹ ABRAMOWITZ E W and SWARTZ W B Arch Dermat & Syph 37:441, 1938

forms, blankets). The skin manifestations assumed many forms, including pruritus, erythema, erythematous dermatitis, eczema-

especially scabies, were important predisposing factors, the eruption maintained by the wool tended to resemble the original condition. The localization of the lesions of the various forms was most varied. In some instances the sensitivity was related to antivermin material impregnated in the textiles, and in some to *Staphylococcus aureus* growing saprophytically in sweat-soaked parts of the underclothing. A number of their patients, particularly those with erythematous eruptions, responded well to administration of vitamin C. Ballester¹⁴⁰ and Mom¹⁴² described cases with intense erythema, conjunctivitis, and respiratory symptoms due to wool allergy, another with angioneurotic edema and urticaria who manifested eczematous responses to patch tests, and 6 with neurodermatitis. All experienced pruritus on contact with wool, most marked on the neck and in the flexures.

In instances of suspected wool allergy, the possibility of sensitivity to dyes, finishes, chromes, mordants, and other substances must be considered (Sulzerbger and Baer⁷²¹). Such cannot be the case, however, in those patients who react to patch tests with all samples of wool (FIG. 175), including specimens from various sources and undyed and unbleached ones.



FIG. 173 ALLERGIC CONTACT DERMATITIS DUE TO WOOL
All areas covered by sweater and not protected by underclothes are involved

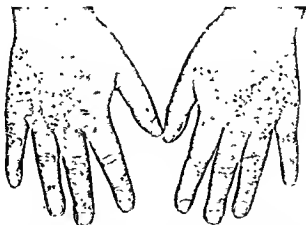


FIG. 174 ALLERGIC CONTACT DERMATITIS DUE TO WOOL
Distribution explained by fact that patient held skeins of wool while they were being rolled

toid dermatitis, circumscribed and diffuse lichenification, facial dermatitis, prurigo simplex, urticaria, and prurigo simulating scabies. Friction with the garments in association with sweating, and some preceding dermatosis,

A thorough review with an extensive bibliography on the subject of dermatitis from

¹⁴⁰ BALLESTERO, L. B., and MLOW, A. M. *Rev argent dermatosis* 21, 40, 1945

wearing apparel has recently been contributed by Schwartz and Peck⁴⁴³. Not only must natural and synthetic fabrics of all kinds be considered but also special finishes, dyes and mordants, mothproofing, lousicides and anti-mildew agents.

Also not uncommon are instances of cutaneous allergy to wool fat or lanolin (Fig. 176) especially in wool sensitive patients (Sulzberger and Morse⁴⁴⁴, Ray and Blank⁴⁴⁵, Urbach⁴⁴⁶) and to cod liver oil as constituents of ointments. Hypersensitiveness to animal hair is occasionally encountered—e.g. to camel's hair (Rowe and Rogers⁴⁴⁷).



FIG. 175 POSITIVE PATCH TEST REACTIONS TO WOOL FROM SEVERAL SOURCES

Including undyed and unleached samples. Indicative of hypersensitiveness to wool itself rather than to dyes, finishing substances, mordants and the like.

The literature on allergic dermatitis to leather has been admirably covered by Beerman⁴⁴⁷. According to this review, hypersensitiveness to leather has occasionally been due to shoes, gloves, jackets, grips of golf clubs, covers on steering wheels and trusses. Here, as in the cutaneous manifestations due to furs or fur-lined gloves, the possibility must be ruled out that the hypersensitiveness is in

relation to the dye, especially para-phenylenediamine. Furthermore, the combination of dermatitis of the feet—due to shoe leather or to leather dyes—with fungous eruptions of the feet is not unusual. However, in the cases of dermatitis due to shoes observed by Shaw⁴⁴⁸, dermatophytosis was not associated. Only one foot may be involved. The differential diagnosis of these two forms of eruption is of great practical importance. Goodman and Sulzberger⁴⁴⁹ point out that in cases of leather dermatitis there is little or no involvement of the interdigital spaces but maximal eruption in the sites of pressure or friction from the shoes, such as the dorsum of the foot, the instep, the heels and particularly the dorsal aspects of the great toes. Moreover, the



FIG. 176 POSITIVE PATCH TEST WITH WOOL FAT (LANOLIN)

procedures usually successful in treating dermatophytosis are unsatisfactory. The itching is also more severe than in uncomplicated dermatophytosis.

Hyperhidrosis is an important contributory factor in shoe leather dermatitis (Dolce⁴⁵⁰) and should be appropriately treated.

It has been pointed out that since almost all commercial shoes contain linings and insoles, little or no contact with the leather may take place. In addition to the leather, Shaw⁴⁴⁸ and Burgess^{450a} list as the possible sensitizers in shoes the compounds used in processing the leather, the lining, canvas, fabricoid, the anti-mildew and fungicide preparations impreg-

⁴⁴³ SCHWARTZ L. and PECK S. M. J. A. M. A. 125: 1209, 1941.
SULZBERGER M. B. and MORSE J. L. *ibid.* 96: 2099, 1931.
RAY L. F. and BLANK I. H. A. J. Dermat. & Syph. 42: 285, 1940.

⁴⁴⁴ ROWE A. H. and ROGERS H. *Californ. & West. Med.* 23: 1589, 1922.

BEERMAN H. *Arch. Dermat. & Syph.* 29: 671, 1934.

⁴⁴⁸ SHAW C. *ibid.* 49: 191, 1914.

⁴⁴⁹ GOODMAN J. and SULZBERGER M. B. J. Allergy 9: 15, 1938.

DOLCE F. A. M. I. Syph. 95: 50, 1944.

^{450a} BURGESS J. F. *Canad. M. A. J.* 47: 27, 1942.

nated in the lining, glue, adhesives, felt, and synthetic substitute materials, dyes, and shoe polishes. Since each manufacturer employs different substances, the patient may sometimes obtain relief by changing his brand of shoes.

According to Norwood and Evans,¹¹⁹ workers wearing leather gloves frequently suffer from eczematoid lesions. They found that the dermatitis was caused by two factors: (1)



FIG. 177 NEURODERMATITIS DUE TO HYPERSENSITIVENESS TO FEATHERS

Dermatosis was controlled simply by elimination of these from environment

the macerating effects of the leather gloves on perspiring skin, and (2) allergic sensitization of the hands due to the presence of epidermophytosis elsewhere on the body.

Artificial leather is also capable of producing allergic contact dermatitis.

Of considerable importance is cutaneous hypersensitiveness to feathers (FIG. 177). Rostenberg and Sulzberger¹²¹ found that goose

feathers elicit positive patch test reactions so frequently in infantile dermatitis that they recommend routine avoidance of feathers in this condition. Vaughan¹²² reported a case of dermatitis of the ears from contact with feather pillows; use of dustproof covers provided relief. The senior author observed a case of dermatitis of the hands and forearms in a man who had to pluck about forty chickens a day. A scratch test to chicken feathers was positive, but not to chicken meat, and the patient could eat chicken. The eruption disappeared when he wore gloves while working. De Besche¹²³ described a similar case.

Animal foods quite frequently elicit skin manifestations by direct contact. Thus Joltrain,¹⁰⁹⁶ Brabant,¹⁴⁵⁷ and Urbach¹⁵⁰³ have observed an urticarial eruption following mere contact with egg white while opening raw eggs.

Contact dermatitis caused by *chicken blood* was described by Newton¹⁴⁵³; and Umansky¹⁴⁵⁴ has observed the same condition caused by beeswax in a beekeeper.

Finally, *dander* from horses, dogs, and other animals must be mentioned as the causative allergens in some cases of dermatitis.

Simon¹⁴⁵⁵ advanced evidence that *human dander* either from the patient's own scalp or from those of parents or others with whom he comes in contact may be a significant cause of infantile dermatitis. He¹⁴⁵⁶ elicited skin reactions with patch tests with human dander in the majority of children with this condition and with neurodermatitis, although adults with neurodermatitis failed to react. These responses would seem to be closely related to those described by Albert and Walzer¹⁴⁵⁷ obtained with silk and feathers.

C. DRUGS

There are three groups of people who not infrequently manifest skin diseases due to contact allergy to drugs: (1) workers engaged in manufacture of drugs, (2) druggists, dentists, physicians, and nurses, who handle these substances; and (3) patients using drugs for

¹⁴⁵³ BRABANT, Y. G. Bull et mém Soc. méd. d. hôp. de Paris 47: 1202, 1923

¹⁴⁵⁴ NEWTON, H. D. Arch. Dermat. & Syph. 34: 492, 1935

¹⁴⁵⁵ UMANSKY, G. I. Dermat. Wchnsch. 98: 177, 1934

¹⁴⁵⁶ SIMON, F. A. J. A. M. A. 125: 370, 1944

¹⁴⁵⁷ Idem. Ann. Allergy 2: 109, 1944

¹⁴⁵⁸ ALBERT, M., and WALZER, M. J. Allergy 14: 347, 1943

¹²¹ ROSTENBERG, A. JR., and SULZBERGER, M. B. Arch. Dermat. & Syph. 35: 433, 1937

external application. Regarding the last group it should be pointed out that the possibility of medicamentous allergization should be considered when a patient's skin condition first shows signs of improvement under external treatment and then for no apparent reason not only ceases to improve but is actually aggravated. Such overtreatment dermatitis has been the subject of recent reports by Gaul¹⁴⁵ and Lane.¹⁴⁶ The former urges the

belladonna plasters bichloride of mercury bichromates butesin picrate calmi tol camphorated oil containing cottonseed oil chloral hydrate coleine cresol emetine hydrochloride ephedrine ethereal oils ethyl aminobenzoate formalin hexylresorcinol iodine iodoform lysol merthiolate metapfen medicated alcohol morphine novocain nupercaine opium phenol phenylhydrazine physostigmine picric acid procaine quinine resorcin



FIG 178 ACUTE CONTACT DERMATITIS

Due to hypersensitiveness to arnica (1 per cent in 70 per cent alcohol)

value of past treatment patch tests in suitable cases as a guide to both diagnosis and rational therapy. The abuse of self applied remedies is probably greatest with respect to dermatitis pedis (Underwood et al.¹⁴⁵)

The following have been more or less frequently reported as contact allergens: ammoniated mercury, arnica (FIG 178), arsphenamine (FIG 179), atropine, balsam of Peru,



FIG 179 LOCALIZED DERMATITIS OF HANDS AND FOREARMS

In nurse whose work was opening arsphenamine ampules. Negative patch test with 1:10 arsphenamine; positive scratch test.

salicylic acid (FIG 180), scarlet red, sulfonamides, sulfur, strychnine, and tar.

In some instances a patient does not react to the individual constituents of a mixture to which he is specifically hypersensitive. For example, he will tolerate 10 per cent ammoniated mercury in petrolatum or 10 per cent salicylic acid in petrolatum but will prove hypersensitive as demonstrated by a patch test to a combination of 5 per cent ammoniated mercury plus 5 per cent salicylic acid. In all probability a new chemical compound is formed to which the patient acquires sensitivity.

Reactions to contact with drugs usually ap-

¹⁴⁵ GAUL, L. E. J. A. M. A. 127: 439, 1944.

¹⁴⁶ LANE, C. G. J. Omaha Mid West Clin Soc. 6: 45, 1945.

pear as erythema or acute dermatitis, rarely as chronic dermatitis, and only exceptionally as urticaria. It is sometimes possible, on the basis of the localization of skin manifestations in a given case, to make a tentative diagnosis as to the identity of the causal substance. Thus, for example, involvement of the axillae directs suspicion to a deodorant, of the genital region, to substances used in the management of pediculosis pubis, of the eyelids, to eye

hands, forearms, and groin appear in a mother after she applied 10 per cent ammoniated mercury ointment to her young daughter's impetigo contagiosa in accordance with her pediatrician's instructions. Only after the child's dermatosis recurred, and as an indirect consequence, the mother's urticaria, was the relationship recognized. Patch tests applied in the usual manner produced a marked whealing response after a few hours.



FIG. 180 ACUTE CONTACT DERMATITIS

Due to hypersensitivity to salicylic acid (0.4 per cent in zinc oxide lotion)



FIG. 181 ALLERGIC CONTACT DERMATITIS

Due to quinine contained in contraceptive jelly used by patient's wife

drops and salves; and a refractory dermatitis on the penis suggests the use of a contraceptive containing quinine (FIG 181)

In some instances it is not the patient himself, but someone in his immediate environment who uses the allergenic drug. Thus Sulzberger reported the case of a man presenting dermatitis of the hands, neck, and genitals, together with a demonstrable hypersensitivity to calmitol—which was used not by him but by his wife. A similar case is that of a mother who suffered contact dermatitis from washing the clothes of a child who had been using a proprietary antipruritic ointment. The junior author has seen urticaria of the

Another interesting source of contact is illustrated in the 2 cases reported by Bass¹⁴⁰. These patients had an eruption of the hips, cheeks, and circumoral regions after teeth were filled with mercury amalgam. In one case, further fillings 2 years later resulted in a generalized urticaria which was relieved within 24 hours by removal of the filling. Markow¹⁴² reported a somewhat similar case of urticaria. Gabel and Kramer,¹⁴¹ in describing cases sensitive to ammoniated mercury ointment and mercury bichloride, note that it is not unusual for a patient to be susceptible to one compound

¹⁴⁰ BASS, M. H. *J. Pediat.* 23: 215, 1943.

¹⁴¹ GABEL, H. and KRAMER, B. *Am. J. Dis. Child.* 64: 15, 1943.

of mercury and not to another, and that the same patient may show different types of reaction depending on the drug used. The extreme degree which hypersensitiveness to mercury may reach is illustrated by the observation of Underwood et al.¹⁶⁶³ that patch tests with a 1:1,000,000 dilution of either organic or inorganic mercurials may produce bullous reactions and even focal flares of distant dermatitis in some cases. Samitz¹⁶⁶² observed a case in which local application of 10 per cent ammoniated mercury produced eczematous contact dermatitis and a generalized erythematous maculopapular eruption of the "id" type, along with chills, fever, nausea, trismus, edema of the entire face, grayish discoloration of the gums, and edema of the gingival tissues. A patch test was markedly positive.

Of outstanding importance as medicamentous contactants are the *sulfonamides* because of their marked sensitizing properties and their widespread use in ointments, creams, powders, proprietary skin remedies, nose drops and sprays, prepared bandages, and other topical applications. One brand of brushless shaving cream even contained 1 per cent sulfathiazole for a time! The fact that local exposure may lead to generalized sensitization, rendering hazardous subsequent systemic administration of the sulfonamides, has been considered elsewhere (p. 329). It should be reiterated, however, that there need not necessarily have been a dermatitis at the time of the original topical application, but if this has been present, the dermatitis may appear initially and more severely at the previously involved sites (Weiner¹⁶⁶⁵). Here we shall consider these drugs only in so far as they act merely as contactants. Recent reviews include those of Brown,^{1155, 1663} Cole¹⁶⁶⁴ and Howell¹⁶⁶⁵.

Abramowitz¹⁶⁶⁶ has listed as the complications ensuing from the external use of sulfonamide compounds (1) development of a local or generalized dermatitis (allergic sensitization), (2) appearance of photosensitization to sunlight and ultraviolet rays, (3) interfer-

ence with the action of roentgen rays (4) delay in wound healing time (5) local sanguineous oozing (6) interference with the action of sulfonamide compounds by local anesthetics of the procaine series and the chemically related vitamin para aminobenzoic acid, (7) resistance to sulfonamide therapy, and (8) rendering the patient vulnerable to the subsequent use of the drug when most needed.

Regarding the first possibility, the manifestations in most instances are those of an acute vesicular dermatitis confined to the sites of contact. Local sensitization appears to be favored when the original condition under treatment is a chronic eczematous process in which sensitization to various substances, including bacteria, has occurred (Livingood and Pillsbury¹⁶⁶⁹), a varicose or stasis dermatitis or ulcer (Cohen, Thomas, and Kalisch,¹⁶⁶⁷ Cole,¹⁶⁶⁴ Howell¹⁶⁶⁵), a burn, a minor surgical injury, or a minor infection of the mucosal orifices. Other factors are an excessive concentration of the drugs, especially above 5 per cent, and continuation of the treatment for periods of time over 5 or 6 days (Erskine¹⁶⁶⁸). Sensitivity does not appear in less than 12 hours (Darke¹⁶⁶⁷), but may require well over a month of treatment. MacGregor¹⁶⁶⁸ found that local latent allergization in 1 case persisted for at least 15 months. A knee injury treated with sulfanilamide healed without incident, but when sulfanilamide powder was applied to a deep abrasion of the buttock 15 months later the same area of the knee became red and, within 36 hours, oozing.

The reported incidence of contact dermatitis from sulfonamides varies considerably about 12 per cent (Livingood and Pillsbury¹⁶⁶⁹), 23 per cent (Robinson and Robinson¹⁶⁶⁹), 3 to 4 per cent (Burgess¹⁶⁶³), 5 to 6 per cent (Darke¹⁶⁶⁷), and about 12 per cent (Goldschlag¹⁶⁷⁰). Among the large series may be mentioned 300 cases of serious cutaneous eruptions in industrial dermatoses reported by Downing¹⁶⁷¹, 100 cases, including several who manifested

¹⁶⁶² SAMITZ M H Arch Dermat & Syph 50 10 1944

¹⁶⁶³ WEINER A L J A M A 123 436 1943

¹⁶⁶⁴ COLE H N ibid 123 415 1943

¹⁶⁶⁵ HOWELL J B Clinics 3 945 1944

¹⁶⁶⁶ ABRAMOWITZ E W Arch Dermat & Syph 50 289 1944

¹⁶⁶⁷ DARKE R A J A M A 121 303 1944

¹⁶⁶⁸ MACGREGOR I M Brit M J 1 414 1943

¹⁶⁶⁹ ROBINSON H M and ROBINSON H M J South M J 34 1093 1941

¹⁶⁷⁰ GOLDSCHLAG F M J Austral 2 3 297 1944

¹⁶⁷¹ DOWNING J G J A M A 120 196 1944

severe generalized rashes following patch tests, by Fisher¹⁷³; 55 cases of dermatitis due to local application, by Tate and Klorfajn¹⁷²; 65 cases, most of which were due to application of sulfonamide powder and possibly the result of inhalation exposure, by Peterkin¹⁷³, and 26 cases by Ellis.¹¹⁶¹ In addition, Park¹⁷⁴ described 12 cases due to various sulfonamide compounds, Miller¹⁷⁵ 5 and Weiner¹⁷⁶ 4 cases due to sulfathiazole ointment, and Sams and Capland¹⁷⁷ an interesting case following application of sulfathiazole powder to the ears. Even infinitesimal doses of sulfathiazole ointment can induce epidermal sensitivity (Becher^{177a}).

Many, if not most of the cases studied gave positive patch tests, although some investigators were unable to elicit them. Shaffer, Lentz, and McGuire,¹¹⁶² in a careful allergic study of 4 cases in whom manifestations of sensitivity were later evoked by oral medication, also reported negative patch tests, but were able to demonstrate positive Prausnitz-Kuestner passive transfers and probable Urbach-Koenigstein reactions. A large percentage of all cases gave evidence of systemic allergization on subsequent administration of the drug.

The clinical picture is frequently complicated by photosensitization. The resultant dermatitis appears, of course, on areas exposed to sunlight. This disorder is less likely to arise in dark-skinned persons or those deeply suntanned. Park¹⁷⁴ found that in 3 of 12 cases of dermatitis the distribution was typical of photosensitive conditions. In Clark's¹¹⁷³ case the opposite circumstances were noted. Once sensitization had been acquired by reason of the local application of sulfathiazole ointment, it appeared that exposure to sunlight predisposed or conditioned the skin to sensitivity to sulfathiazole since the dermatitis appearing after internal administration of the drug was definitely limited to unclothed areas. Pa-

tients under sulfonamide therapy, whether topical or systemic, should be warned against exposure to the sun.

Manifestations other than acute dermatitis have been recognized. Apparent exacerbation of the pre-existing dermatosis being treated or a tendency to mimic its appearance has been noted following the external use of sulfonamides. Such isomorphic reaction (Koebner phenomenon) has been noted in psoriatic patients by Howell.¹⁷⁶⁰ In other cases the eruption may be chronic and may assume the characteristics of an epidermolysis (Darke¹⁷⁶⁷). When the scalp is involved in dermatitis there may be temporary loss of hair. Cohen, Thomas, and Kalsch¹¹⁶⁷ observed 2 cases with fever and a generalized rash following application of 5 per cent sulfathiazole ointment to varicose ulcers of the leg, while Kalz and Steeves¹¹⁷² reported 2 cases with marked local edema accompanying an oozing dermatitis due to the application of 30 per cent sulfathiazole in a glycerin base for syphilis barbae. Patch tests in the latter cases were positive with several different sulfonamides, but only on previously affected areas. The fact that systemic allergization need not always include epidermal sensitivity is illustrated by the patient of Green and Steckel.¹¹⁸⁰ Although fever and a generalized morbilliform rash followed oral administration of sulfathiazole for the treatment of a staphylococcal leg lesion, local application of a 5 per cent sulfathiazole ointment was tolerated without reaction, although the blood level reached almost 1 mg. per 100 cc.

Successful hyposensitization by the oral route of 12 cases of cutaneous sensitivity to sulfonamides was reported by Tate and Klorfajn.¹⁷²

Penicillin is much less likely to produce epidermal sensitization than are the sulfonamides. Most of the reports of contact dermatitis due to this drug concern medical officers, physicians, or others handling the powder or solutions. Thus the first such case, described by Pyle and Rattner,¹¹⁸¹ was a medical officer who prepared and administered penicillin. Preceded by a mild marginal blepharitis and

¹¹⁷² TATE, B. C., and KLORFAJN, I. *Lancet* I, 39, 1945

¹¹⁷³ PETERKIN, G. A. G. *Brit. J. Dermat.* 57: 1, 1945.

¹¹⁷⁴ PARK, R. G. *Brit. M. J.* 2, 69, 1943

¹¹⁷⁵ MILLER, J. R. *Arch. Dermat. & Syph.* 46, 379, 1942

¹¹⁷⁶ WEINER, A. L. *J. A. M. A.* 121: 411, 1943

¹¹⁷⁷ SAMS, W. M., and CAPLAND, L. *Arch. Dermat. & Syph.* 44, 226, 1942

^{1177a} BECHER, P. E. *Pennsylvania M. J.* 49, 417, 1946

¹¹⁷⁸ CLARK, T. W. *J. A. M. A.* 123, 9-9, 1943

¹¹⁷⁹ KALZ, F., and STEEVES, L. C. *J. Allergy* 14: 79, 1942

¹¹⁸⁰ GREEN, R. C., and STECKEL, M. L. *J. A. M. A.* 122: 296, 1943.

¹¹⁸¹ PYLE, H. D., and RATTNER, H. *Ibid.* 125, 903, 1944

conjunctivitis, dermatitis soon appeared on the face, and later on the hand and genitalia. Comparable cases were reported by Binkley and Brockmole,¹⁴⁸ Silvers,¹⁴⁹ Barker,¹⁵⁰ and Bechet.^{1477a} Patch tests in these patients were almost all positive. Although these reactions are usually attributed to impurities in the available supplies of the drug Pyle and Rattner's case reacted to tests with a crystal line preparation but not to the culture medium on which the mold was grown, indicating that the dermatitis was due to the penicillin itself.

Dermatitis of the eyelids following instillation of penicillin sodium into the conjunctival sac was reported by Keyes,¹⁴⁸ Selinger,¹⁴⁹ and Nelson and Sandt.¹⁴⁸ Patch tests were negative. Morton¹⁴⁵ mentions several cases of contact dermatitis in patients. However, despite the use of penicillin sodium in various ointment bases and of aqueous solutions of penicillin calcium in topical therapy on a considerable number of patients, one of us has never seen a case of contact dermatitis result from this treatment or manifest a positive patch test. It should be pointed out that solutions of penicillin sodium are rather alkaline in reaction, and capable of causing non allergic irritation for this reason.

There is no evidence that epidermal sensitization from penicillin—unlike that due to the sulfonamides—predisposes to general allergization when the drug is administered systemically later. However, in one physician whose case was described earlier and who suffered contact dermatitis of the hands from handling penicillin and some months later of the eyelids and cheeks from penicillin eye drops, subsequent intramuscular administration after an interval of three months caused a vesicular flare of all the previously affected sites as well as of some other areas.

As an interesting example of occupational exposure to drug contactants—among many others which might be cited—may be men-

tioned the recent report of Dore and Thomas.^{1 2} In a London morphine factory 9 cases of contact dermatitis were seen among a total group of 18 employees. Aside from one man with serotal involvement and another in whom the eruption eventually became generalized the dermatitis affected only exposed parts of the body. The clinical appearance varied considerably. On the face and neck it was usually diffuse and of typical contact type and on the hands it was sometimes cheirropompholyx like, while in one case it resembled erythema multiforme. It was not possible to identify the specific sensitizer, but it might have been an impurity.

Drugs contacting mucous membranes are capable of producing not only specific local reactions, examples of which will be cited in various chapters of the third part of the book, but also the most severe allergic manifestations. Thus, Thomas and Fenton¹⁴⁸ reported 3 deaths and 4 severe constitutional reactions following the use of *pontocaine* for surface anesthesia in bronchoscopy and gastroscopy, and Hansen and Stealy¹⁴⁹ another death from the same cause. Spencer¹⁴⁹ described an acute erythematous papulovesicular eruption around the nostrils and upper lip, along with discrete erythematous papular lesions over most of the body, due to *ephedrine* in oily nose drops. Topical application of *argyrol* to the nose produced sneezing, rhinorrhea, nasal obstruction, and asthma in a patient observed by Crip.¹⁴⁹ An intracutaneous test resulted in a severe local and a mild constitutional reaction, and passive transfer tests were positive. Crip suggests that argyrol may be a frequent cause of sensitization, accounting for the discomfort experienced by some patients after its use. Wolf^{150a} has observed that in allergic patients colloidal silver solution nasal tamponage often aggravates the symptoms.

Sensitivity to *tyrothricin*, an antibiotic prepared from a soil mold, has not as yet been reported. However, one of the writers' patients with mold rhinopathy and mold asthma

¹⁴⁸ BINKLEY G W and BROCKMOLE A. Arch. Dermat. & Syph. 50: 326, 1944.

¹⁴⁹ SILVERS J H. ibid. 50: 378, 1944.

¹⁵⁰ KEYES J E L. J. A. M. A. 126: 610, 1944.

^{1477a} SELINGER E. ibid. 128: 437, 1945.

¹⁴⁸ NELSON L M and SANDT K E. N. Bull., North African Theater Opns. U. S. A. 2: 62, 1944.

¹⁴⁵ MORTON W. cited by FOGLEY K D. Letters Internat. Coll. Club of Allergy. Series 8: 41, 1945.

¹⁴⁸ THOMAS J W and FENTON M M. J. Allergy 14: 140, 1943.

¹⁴⁹ HANSEN F M JR and STEALY C L. Rev. Gastroenterol. 10: 212, 1943.

¹⁴⁹ SPENCER G A. Arch. Dermat. & Syph. 51: 48, 1945.

¹⁴⁷ CRIP L H. J. A. M. A. 121: 421, 1943.

^{150a} WOLF G D. ibid. 130: 2: 3, 1946.

had a violent nasal and bronchial reaction after local nasal use of prothricin (a combination of tyrothricin and paredrine), but not after paredrine alone.

D. COSMETICS

Cosmetics are occupying an increasingly important place as contactants (Downing¹²⁷). They embrace such a variety of substances as



FIG 182 ALLERGIC CONTACT DERMATITIS
Due to volatile oils used as flavoring in tooth paste

perfumes, volatile oils (FIG. 182), toilet waters, sachet powders, scented soaps, face and body powders, creams (cleansing, foundation, tissue, cold, vanishing, massage, scalp, bleaching), hand lotions, face packs, hair oil, hair tonic, hair lotions, hair dressings, hair dyes (aniline, metallic, vegetable), pigments, wave-set, shampoo, eye shadow, eyebrow pencil, eyelash ointments, artificial lashes, lipstick, rouges, nail polish, polish remover, deodorants, anhidrotics, depilatories, and wrinkle removers. Finally, the ingredients of douches should be kept in mind.

Aside from the improper use of depilatories, cuticle removers, perspiration inhibitors, bleaching and freckle creams, hair wavers and straighteners which contain primary skin irritants, the majority of dermatoses among the users of cosmetics belong to the allergic class (Schwartz¹²⁸). Table 36 lists the cosmetics commonly responsible for dermatitis. Interestingly, workers manufacturing them are rarely affected, but among beauticians and the general public it is a different story. Among numerous other substances cottonseed oil is contained in some cosmetics, and patients sensitive to it should receive appropriate warning.

The factors in cosmetics that may cause dermatitis are chiefly as follows:

Perfume (synthetics and natural products such as gums, barks, mosses, citrus oils, flower extracts, and animal substances)—found in all types of cosmetics

Indelible dye (an aniline)—found in lipsticks only
Coloring matter (lakes and other anilines)—found chiefly in nail polish, lipsticks, rouges and powders and occasionally in creams and lotions

Vegetable substances—found in all types of cosmetics

Fats and oils—cocoa butter, coconut oil, castor oil, cottonseed oil, etc.

Gums—tragacanth, karaya, quince seed, etc.

Powders—orris root, rice powder, etc.

Miscellaneous substances—such as beeswax and lanolin—found in all types of cosmetics

The circumstances under which patch tests or clinical tests may be made should also be considered since perfumes and dyes sometimes may be irritating only when activated by sunlight. Other physical agents may also play a part in the activation of otherwise innocuous substances. Still another point to be considered is that certain substances, innocuous in themselves, may prove irritating in combination. Moreover, in taking the case history of the cosmetic sensitive patient the physician should avail himself of any clues pointing to factors outside the cosmetic field. Thus, allergens which are normally found in cosmetics may also be found in such products as toothpastes, toothpowders, gargles, medicated salves, nasal jellies and sprays, foods, fruits.

¹²⁷ DOWNING, J. G. *ibid.* 182: 2082, 1934

¹²⁸ SCHWARTZ, L. J. *Am. Pharm.* 5: 74, 1944.

TABLE 36—*Cosmetics Reported to Have Caused Dermatitis (Schwartz,¹⁴⁹³)*

Cosmetics	Chemical Causes	Type of Dermatitis	Comparative Frequency
Creams	Petrolatum Triethanolamine Methyl heptene carbonate Phenols Mercurials	Allergic	Rare
Deodorants	Aluminum salts	Primary irritant and sensitizer	Fairly common
Depilatories	Thallium acetate (system poison)	Primary irritant	Fairly common
Hair wavers, straighteners, and lacquers	Alkalis Resins	Primary irritant and sensitizer	Fairly common
Hair dyes and eyelash dyes	Oxidation dyes i.e. Paraphenylenediamine Paratoluidine Orthoamido phenol Paratoluenediamine Metatoluenediamine	Allergic	Now rare but frequent when these dyes were first introduced
Lipstick	Dyes, chiefly the eosin group which are photosensitizers Perfume methyl heptene carbonate	Allergic	Fairly common
Nail lacquers	Synthetic resins of formaldehyde and ester gum types Dyes, eosin Rhodamine B and Deep Maroon	Allergic	Fairly common
Perfume	Oil of bergamot Methyl heptene carbonate Synthetic jasmine Linalool Eugenol Copper	Allergic	Rare
Powders	Orris root Dye	Allergic	Rare
Soaps cleaners, synthetic detergents	Alkalis Phenols	Defatting action on skin and sensitizer	Fairly common

candies, chewing gum, antacids, and medicines for internal and topical use

Several manufacturers of hypoallergenic cosmetics will on request furnish samples of the individual ingredients of their preparations, enabling the physician to determine the offending agent and to select or formulate a cosmetic harmless to the particular patient. In certain cases mere omission of the scent will be all that is necessary.

Some of the more common perfumes, used

as such or in soaps, include the following oils (Schwartz and Tulipan¹⁴⁹⁴)

anise	lavender
bergamot	peppermint
bitter almond	rosemary
cananga	saffron
caraway	sassafras
cinnamon	sweet orange blossom
citronella	terpineol
clove	thyme
geranium	

Bergamot oil appears to be of special importance. Freund was the first to show that a pigmentation on the neck and upper part of the back (FIG. 183) and chest was attributable to exposure to sunlight following application of eau de Cologne in which bergamot oil was found to be the allergenic agent. Since these streaks of pigmentation resemble in form the trinkets or charms often attached to necklaces and watch chains, Rosenthal coined the term "berloque dermatitis" to designate this condition. According to the experimental investigations of Zurhelle and others, the ethereal oils are dissolved by sweat, thus releasing pho-

agent of dermatitides seems to be nail polish. Nail lacquers are highly complex mixtures containing many ingredients that are potentially allergizing, including a base of cellulose nitrate or pyroxylin which is itself not a single chemical but a series of nitrocelluloses, mixtures of solvents, plasticizers to promote flexibility, gums and resins to increase adhesive properties and luster and also to prevent cracking and chipping, various dyes, and perfumes to mask the odors of these mixtures. Despite extensive investigation, no single ingredient of nail lacquer has been established as responsible for the bulk of cases. Osborne et al.¹⁴⁹⁵ held that



FIG 183. LOCAL LIGHT HYPERSENSITIVENESS

Due to cutaneous allergization by bergamot oil contained in eau de Cologne (berloque dermatitis)



FIG 184 CHEILITIS DUE TO HYPERSENSITIVENESS TO LIPSTICK

tosensitizing substances; the dermatitis arises, therefore, where sweat has run down. The persistent pigmentation makes the condition especially annoying.

Lipstick has been recognized as a frequent cause of contact cheilitis (FIG 184). Goodman and Sulzberger¹⁴⁴⁹ pointed out that this condition is caused chiefly by the dye tetra-bromofluorescein. It must be noted, however, that in some cases it is the perfume and not the dyes in the lipstick that causes the cheilitis. Some dyes and perfumes may be allergenic only when activated by sunlight and this fact must be kept in mind in performing patch and clinical tests. In addition, Hathaway¹⁴⁹⁴ has reported 2 cases of dermatitis in which traces of the metallic containers of lipsticks were found to be the allergenic agents.

Among the cosmetics, the most frequent

the allergen is generally the dye, perfume, fixative, or plasticizer. Dobes and Nippert¹⁴⁹⁶ obtained positive patch test reactions in 30 cases with resins, dyes, and nitrocellulose, but concluded that the solvents are the usual cause, no reactions were elicited by camphor plasticizer, ethyl acetate, butyl acetate, or butyl alcohol. They found that nearly all their patients could tolerate with impunity some brand of nail polish, especially a colorless one, other than the one producing the dermatitis. Shelton¹⁴⁹⁷ reported a case due to colorless nail polish foundation, thus acquitting the dye as regards this patient. Simon's¹⁴⁹⁸ thirteen cases failed to react to dye, but for-

¹⁴⁹⁵ OSBORNE, E. D., JORDON, J. W., and CAMPBELL, P. C., JR. *Ibid.* 44: 601, 1941.

¹⁴⁹⁶ DOBES, W. L., and NIPPERT, P. H. *Ibid.* 49: 183, 1944.

¹⁴⁹⁷ SHELTON, J. M. *Ibid.* 48: 197, 1943.

¹⁴⁹⁸ SIMON, F. A. *South. M. J.* 36: 157, 1943.

¹⁴⁹⁴ HATHAWAY, J. G. *Arch. Dermat. & Syph.* 43: 703, 1941.

maldehyde-sulfonamide resin was found to be the most important allergen in the polish. According to Keil and Van Dyke¹⁴⁹⁹ toluene sulfonamide resin is the chief cause of nail polish dermatitis as seen today, while the bases, plasticizers, coloring matter, solvents, and perfumes rarely cause trouble. Hypersensitive ness to this resin is frequently accompanied by group reactions to related chemical fractions and derivatives, extending even to sulfanil amide on the basis of tests on one patient.

The usual localization of nail lacquer dermatitis is not, as one might assume, the fingers or the hands, but rather the following sites, at least in women: eyelids, corners of mouth, chin, nares, sides of neck, cheeks, ears, ear canals, shoulders, and chest. Less common sites are the thighs, antecubital spaces, axillae, and anogenital area. Of the eyelids, the upper are more commonly involved, on one or both sides, and most frequently the medial portion, at least initially. Considerable edema may be present in this region. (According to Hazen,¹⁴⁹¹ other causes of allergic dermatitis of the eyelids include orange peel, carbon paper, wave set lotion, hair dye, face powder, dog hair, cold cream, and ammoniated mercury.) Two facts account for the failure of lesions to appear on the hands, and their presence in the areas mentioned. For lesions to appear on the fingers would require an exposure time of 12 to 24 hours, a requirement which is seldom met because of the prompt removal of the polish from these regions by polish remover (Keil, Russo, and Van Dyke¹⁵⁰⁰), while the thin skin of the eyelids and neck is apparently more readily sensitized than the thicker epidermis of the fingers. The allergen reaches other areas from the hands, such actions as resting the chin on the flexed fingers, rubbing the eyes, biting the nails, and probing the nares and ears with the finger tips "carrying" the dermatitis. The use of nail polish to stop "runs" or "ladders" in stockings may result in a bizarre distribution of the lesions. Bowen points out that toenail polish remaining in shoe linings may account for otherwise unexplainable flares.

Nail lacquer dermatitis is usually of a patchy

low grade erythematous variety. Unfortunately, patch tests with nail polish may sometimes be negative although discontinuance of the use of it will result in a prompt clearing of the eruptions (Burgess¹⁵⁰¹). Osborne et al.,¹⁴⁹⁵ Dobes and Nippert¹⁴⁹⁶ like wise agree that patch test results are regrettably not conclusive in cases of dermatitis due to nail polish. That the dermatitis need not require use by the patient herself but merely close contact with someone who has on nail polish is illustrated by the case of Madden¹⁵⁰², recurrences appeared after the patient had slept with a friend.

Hair lacquers, used by women to maintain their hair styles and applied either as a spray or by means of pads, can also be responsible for contact dermatitis, usually involving the back of the neck, the ears, the adjacent portions of the cheeks, and the eyelids. When shellac became unavailable for these products, substitution of synthetic resins, also employed in wood varnish, greatly enhanced the sensitizing properties, although alkalinity and acidity of the products aided the penetration of the resin into the skin (Schwartz¹⁵⁰³). Typical cases were reported by Downing,¹⁵⁰⁴ Howell,¹⁵⁰⁵ Epstein,¹⁵⁰⁶ and Hailey.¹⁵⁰⁷ Unless previous sensitization has taken place an interval of 7 to 9 days after the initial application seems to be required as a latent period. Although some cases were also sensitive to nail lacquer, there is no evidence that any definite cross-relationship exists, but a patch test with p-toluene sulfonamide formaldehyde resin is suggested to clarify this point (Keil¹⁵⁰⁸). Sites distant from the application may also be affected as the hands and forearms on which the patient's head may rest during sleep. Plotz¹⁵⁰⁹ has observed dermatitis of exposed parts in 2 infants due to contact with the lacquer on their mothers' hair. Certain of the offending preparations have already been withdrawn from the market.

¹⁴⁹⁹ BURGESS J F. *Canad Nl A J* 43: 544, 1940.

¹⁵⁰⁰ MADDEN J F. *Arch Dermatol & Syph* 49: 197, 1944.

¹⁵⁰¹ SCHWARTZ L. *Pub Health Rep* 58: 1623, 1943.

¹⁵⁰² DOWNING J G. *Arch Dermatol & Syph* 44: 465, 1941.

¹⁵⁰³ HOWELL J B. *J A M A* 123: 408, 1943.

¹⁵⁰⁴ EPSTEIN S. *ibid* 123: 409, 1943.

¹⁵⁰⁵ HAILEY H. *South M J* 37: 37, 1944.

¹⁵⁰⁶ KEIL H. Correspondence. *J A M A* 123: 857, 1943.

¹⁵⁰⁷ PLOTZ M. *Am J Otol Chld* 48: 409, 1944.

¹⁴⁹⁹ KEIL H and VAN DYKE L S. *Arch Dermatol & Syph* 50: 39, 1944.

¹⁵⁰⁰ KEIL H, RUSSO J J and VAN DYKE L S. *ibid* 48: 612, 1943.

Of the other cosmetics, recent reports implicate "cold permanent wave," consisting of different detergents and chemicals to curl the hair without using heat, the allergen being contained in the "preliminary lotion" (Howell¹⁵¹⁰); and leg make-up, the offending agent being a red pigment (Ellis¹⁵¹¹).

Triethanolamine, which is used as an emulsifier in brushless shaving and skin creams, was reported in 2 instances as a cause of allergic dermatitis (Curtis and Netherton¹⁵¹²).

A case reported by Hollander¹⁵¹³ clearly illustrates how difficult it may sometimes be to identify the cosmetic at fault. In a case of vesiculo-erythematous lesion involving the nose, the upper lids, and the adjacent portions of the right lower eyelid, patch tests performed with various cosmetics used by the patient were consistently negative; finally, a test made with the rubber sponge puff used by the patient proved to be strongly positive. Elimination of the rubber puff resulted in complete disappearance of the lesion.

E. CHEMICALS

It is not within the scope of this section to catalogue and discuss in detail all the chemicals that have been found to act as allergens. For more exhaustive treatment of the subject, the reader must refer to monographs, such as the excellent textbooks on occupational diseases by Schwartz¹⁵¹⁴ and Prosser White,¹⁵¹⁵ as well as special pamphlets, such as that entitled *Skin Hazards in American Industry*, by Schwartz.^{1516, 1517} Here we shall endeavor to describe only the most important allergenic chemicals. Many of the others are listed in the table of concentrations in the Appendix.

DYES

Dyes quite commonly cause contact dermatitis, contact urticaria, and sometimes also lichen simplex chronicus and photosensitivity (Epstein¹⁵¹⁸). Dyes are widely employed in coloring fabrics for various articles of clothing (dresses, coats, overcoat collars, linings of

suits, hats, hatbands, jumpers, scarves, underclothing, stockings, socks, shoes, shoestrings, garters). They are, however, encountered not only in wearing apparel but also in many other common environmental articles, such as the varnishes on furnitures, in upholstery hangings, draperies, carpets, leather goods, hair dyes, powders, creams, lotions, dentifrices, rouges, lipsticks, newspapers and their rotogravure supplements, wooden handles of kitchen knives, and stained surfaces on which the patient steps barefooted.

This enumeration will show how difficult it is to escape dye contact in a case of polyvalent dye reactivity, such as that described by Simon and Rackemann.¹⁵¹⁹ Dye hypersensitivity can be so great that mere proximity to the substance on the part of a worker in an aniline plant will elicit severe dermatitis in his child (Urbach¹⁵²⁰); or dermatitis in a woman may be maintained by contact with the hands of her husband, a fur dyer, despite every effort to clean his hands by the use of strong chemicals and soap (Niles¹⁵²¹).

To determine whether the sensitivity is in relation to a water-soluble dye rather than to a fabric itself or to some other constituent, it is only necessary to soak a portion of the suspected textile in a small amount of water for a while until the dye "runs," and then perform a patch test with the solution. Kadisch¹⁵²² reported a pertinent case hypersensitive to the lining of his suits and reacting to the water in which the lining was washed. Although the allergen may be present originally in the material of a single suit, it may "contaminate" shirts and underwear, and thus be indirectly brought into contact with the skin.

The allergy may be a reaction to the finished dyes, the dye intermediates, or the basic materials. As an example, Schwartz and Dunn¹⁵²³ traced an outbreak of dermatitis among employees of a woolen mill to the mordanting solution (sodium dichromate) and wetting agents used in the dye bath. Moreover, Sulzberger and Hecht¹⁵²⁴ proved that in some instances impurities, rather than the dye itself (e.g., in

¹⁵¹⁰ HOWELL, J. B. *Arch. Dermat. & Syph.* 49: 432, 1944.

¹⁵¹¹ ELLIS, F. A.: *ibid.* 49: 197, 1944.

¹⁵¹² CURTIS, G. H., and NETHERTON, E. W.: *ibid.* 44: 729, 1940.

¹⁵¹³ HOLLANDER, L. J. *J. A. M. A.* 115: 2771, 1940.

¹⁵¹⁴ SCHWARTZ, L.: *Skin Hazards in American Industry*, pt. 1, Pub. Health Bull. 215, 1934, pt. 2, *ibid.* 229, 1936.

¹⁵¹⁵ EPSTEIN, E.: *Arch. Dermat. & Syph.* 41: 1044, 1940.

¹⁵¹⁶ SIMON, F. A., and RACKEMANN, F. M. *J. A. M. A.* 102: 127, 1934.

¹⁵¹⁷ NILES, H. D.: *Arch. Dermat. & Syph.* 43: 698, 1941.

¹⁵¹⁸ KADISCH, E. L.: *New York State J. Med.* 43: 1051, 1943.

¹⁵¹⁹ SCHWARTZ, L., and DUNN, J. E.: *Indust. Med.* 11: 432, 1942.

¹⁵²⁰ SULZBERGER, M. B., and HECHT, R.: *J. Allergy* 12: 129, 1941.

cosmetic dyes) are the agents. The practical importance of this observation is of course obvious. Likewise resorcin a phenolic compound is an ingredient of certain dyes and may be present in incompletely combined form or in excess a patient hypersensitive to resorcinol may develop dermatitis from contact with fabrics containing such dyes.

Paraphenylenediamine (ursol) has been found to be particularly dangerous. This is a



FIG 183 ALLERGIC CONTACT DERMATITIS IN FURRIER
Due to paraphenylenediamine

black dye extensively used on furs, clothes, hats, and leather, and formerly also for coloring hair. This chemical has been found to be the cause of countless cases of dermatitis (FIG 183) in furriers and tailors, and until recently in hairdressers and in women who had their hair dyed black.

The skin lesions are generally the same as those of contact dermatitis of any cause, including erythema, papule formation, vesiculation, weeping, crusting, and scaling, as well as various degrees of edema. The distribution depends primarily on where the contact takes place (e.g., a dress) as well as to a certain

extent on contributory factors promoting the allergization—for example perspiration in the axillae. According to Bonneve⁹² and to Goodman¹³⁹ and their associates, woman's dress dermatitis presents a fairly characteristic picture affecting generally the periaxillary regions—sparing the pits—the sides of the neck, and the antecubital spaces. In the more severe cases the eruption also spreads over the intervening areas so that the entire upper portion of the body may be involved. In men the eruption usually starts on the legs, extending from the ankles to the lower edges of the underwear, including the popliteal spaces.

Although carbon paper rarely acts as a contactant, Hazen¹⁴⁰ reported dermatitis of the eyelids from this cause, with recurrence following exposure to the smoke of burning carbon paper when a waste basket accidentally caught on fire. The inks employed by mimeographing machine operators and particularly dye removers employed to remove the indelible ink stains from the skin may be a source of irritation.

Cheilitis due to the dyes in lipsticks is discussed on page 666.

Asthma due to the cutaneous resorption of a dye (orange I) contained in tincture of metaphen was described by Criepe¹⁴². The diagnosis was confirmed by both urticarial and asthmatic responses to a patch test with the dye.

RESINS, LACQUERS AND PLASTICS

Severe outbreaks of dermatitis caused by wearing such fabrics as those in brassieres, house dresses, pajamas, shorts, underwear, and stockings have been observed during the past few years in the United States and Canada. Schwartz¹³⁹ and his associates¹⁴³ proved that a particular synthetic resin finish (an emulsion of an acid ester gum—e.g., a combination of natural resins with glycerin) commonly used in the manufacture of such articles of wearing apparel was the cause of these conditions. Clinically, the dermatitis is sharply demarcated over the areas of contact and is characterized by intense pruritus and papule formation, rather than vesiculation (Neilson and

⁹² BONNEVE P. and GEAHER V. A. b. Dermat. & Syph. 34: 220, 1936.

¹³⁹ CRIEPE L. H. J. A. M. A. 105: 1, 69, 1937.

¹⁴⁰ SCHWARTZ L. J. Invest. Dermat. 4: 49, 1941.

Reiches¹²⁴¹). In 20 cases observed by Costello and Ryan¹²⁵⁵ due to resin processed underwear shorts there was also swelling and painful edema of the penis and scrotum. Washing of the garment before wearing failed to prevent the dermatitis. Keil¹²⁵⁶ showed that the various "finishing" substances vary in their sensitizing properties, and that the presence of a wetting or emulsifying agent, such as lauryl sodium sulfate or triethanolamine oleate, enhances the sensitization.

There are 8 principal types of synthetic resins manufactured in the United States, and of these the phenol-formaldehyde and the urea-formaldehyde resins, sold under a number of trade names, are predominant in the quantity of production and the skin hazards involved (Lockey¹²⁵⁷). Over 2600 different articles are manufactured from synthetic resins. They give lacquer its consistency and resistance. They are the cause of innumerable cases of allergic contact dermatitis. Aside from nail lacquer, hair lacquer, and clothing finishes, all discussed above, they are encountered in some of the following objects: bottle caps, buttons, artificial jewelry of various kinds, spectacle frames, steering wheels, artificial dentures, ear pieces of hearing devices, radio and telephone receivers, instruments (physicians', dentists', etc.), wrist watch straps, garter straps, belts, and "plastic" articles of all kinds. Sulzberger¹²⁵⁸ points out that even finished plastic articles often emanate or give into solution at the skin sufficient resins or formaldehyde to cause a severe dermatitis in hypersensitive persons. Patients often give skin reactions not alone to a formaldehyde type of resin in plastics, but also to 5 per cent solutions of formalin, necessitating avoidance of all formalin contacts. In other cases, however, the hypersensitiveness is directed not to formalin but to other fractions of the resin, such as gum esters.

Acute dermatitis due to contact with garters, suspenders, and wrist watch straps made of "elastiglass" (a trade name for a derivative of

vinyl resin) was described by Zeisler,¹²⁵⁹ Zakon,¹²⁶⁰ and others. Schwartz, Peck, and Dunn¹²⁶¹ found that synthetic resin glues or adhesives used in the wood substitute industry, including the making of plywood for planes and gliders, were responsible for occupational dermatitis, acting both as sensitizers and as primary skin irritants. Also, contact with even the minute quantities of resin used in the lining of new tin cans can evoke dermatitides among workers handling these (Schwartz and Russell¹²⁶²). Finally, stomatitis has been increasingly seen by dentists since synthetic resins have come into use in dental prosthesis (Fig. 186).



FIG. 186. POSITIVE PATCH TEST WITH PLASTIC USED FOR DENTAL PLATE

Nitrocelluloses, identical with those used in nail polishes are widely employed in industry—generally in combination with solvents, plasticizers, gums, varnishes, resins, and pigments. They are found, for instance, in the finishes of such common objects as imitation leather, furniture, hairpins, wooden jewelry, umbrellas, pencils, cigarette boxes, toys, and waterproof fabrics (Osborne¹²⁶³). Lacquers are also used in or on such articles as motor car parts (steering wheels, etc.), phonograph records, glass and metal goods, hats (particularly straw hats),

¹²⁵⁴ NEILSON, A. W., and REICHES, A. J. *Arch. Dermat. & Syph.* 44: 218, 1941.

¹²⁵⁵ COSTELLO, N. J., and RYAN, J. E. *Arch. Dermat. & Syph.* 46: 234, 1942.

¹²⁵⁶ KEIL, H. *J. Allergy* 14: 477, 1943.

¹²⁵⁷ LOCKEY, S. D. *ibid.* 15: 158, 1944.

¹²⁵⁸ SULZBERGER, M. B., discussion to LOCKEY, ¹²⁵⁷

¹²⁵⁹ ZEISLER, E. P. *J. A. M. A.* 114: 2540, 1940.

¹²⁶⁰ ZAKON, S. J. *Arch. Dermat. & Syph.* 43: 548, 1941.

¹²⁶¹ SCHWARTZ, L., PECK, S. M., and DUNN, J. E. *Pub. Health Rep.* 58: 879, 1943.

¹²⁶² SCHWARTZ, L., and RUSSELL, J. P. *J. A. M. A.* 113: 448, 1940.

feathers hair pins lacquered objects used in games toilet seat and other paints and furniture lacquers. Their importance as possible allergizing agents should not be overlooked.

Soy bean plastics are already in use in the manufacture of automobile parts and there are indications that they will be utilized even more extensively in the future. Other sources of soy bean contactants are varnish paint enamels printing ink celluloid linoleum paper sizing and massage creams.



FIG. 187 ALLERGIC CONTACT DERMATITIS DUE TO ROSIN ON VIOLIN BOY.

Left side chiefly involved as result of more direct contact.

Rosin (natural resin) was found to be the chief irritant in adhesive plaster (Schwartz and Peck¹⁵³³) as well as an important cause of dermatitis in woodcutters. The rosin on a violin bow can also be responsible for allergic contact dermatitis (Fig. 187).

RUBBER

Rubber is the coagulated latex or milky juice of certain tropical plants. Rubber goods such

as dress shields condoms face pieces of respirators gas masks dental plates surgeons gloves girdles sanitary belts garters trusses bed sheetings hard rubber stethoscopes rubber coverings of eyelash curlers bicycle grips erasers and even rubber sponge powder puffs have been reported to be the causal agents in contact allergies. While sometimes the rubber per se is the allergen there are many other cases in which the sulfur monochloride used in vapor curing or accelerators or antioxidants of a complex chemical nature have been found to be the eczematogenic agents (Obermayer¹⁵³⁴). This differentiation is of the greatest practical importance for in the latter cases soaking of the object in a mild alkaline solution of soap and sodium carbonate and subsequent rinsing in water serve to remove the irritating factor (Schwartz and Andrews¹⁵³⁵). In a series of cases reported by Bonnevill and Marcussen¹⁵³⁶ rubber footwear and articles of clothing accounted for the majority of cases of dermatitis. Etiologically the rubber itself was subordinate in relation to the accelerator agents especially mercaptobenzothiazole used in its manufacture. Cold vulcanized rubber was often tolerated in cases in which there was only accelerator hypersensitivity. Although it is true that the allergic response to rubber almost always takes the form of some cutaneous manifestation Stern¹⁵³⁷ has described a case of severe urticaria and angioneurotic edema that was cured only by the elimination of a hard rubber dental plate.

The complexities of rubber glove dermatitis and the numerous predisposing and contributory causes thereof are well covered in a discussing article by Stokes, Lee and Johnson.¹⁵³⁸ Only a total evaluation of the patient his personal and family background habitus skin type vasomotor mechanism diet autonomic nervous system psychosomatic influences environmental and ingested exposure to allergens infections fungous diseases and other factors will allow a proper understanding and a successful therapy of what may appear to be a

¹⁵³⁴ OBERMAYER FR. M. E. *Arch. Dermat. & Syph.* 27:2, 1933.

¹⁵³⁵ SCHWARTZ L. and ANDREWS G. C. *J. Invest. Dermatol.* 1:219, 1939.

¹⁵³⁶ BONNEVILLE P. and MARCUSSEN P. V. *Acta dermat. venereol.* 25:111, 1944.

¹⁵³⁷ STERN G. *Klin. Wochenschr.* 6:1096, 1927.

¹⁵³⁸ STOKES J. H., LEE W. E. and JOHNSON H. M. *J. A. M. A.* 123:19, 1945.

simple contact dermatitis due to rubber gloves. Undoubtedly similar considerations hold with respect to troublesome and treatment-resistant contact dermatitides of other regions due to other causes. Anderson¹⁵¹ points out that sensitivity to rubber gloves should not be ruled out until patch tests have been performed on the back of the hands. He also noted that rubber dermatitis of the feet is not uncommon in women since rubber cement and elastic rubber fabric are used extensively in the manufacture of women's shoes. It may involve any part of the foot, but most frequently appears first on the toes or the sides of the heels, and may simulate acute dermatophytosis.

As regards synthetic rubber, Schwartz¹⁵² has observed comparatively little dermatitis in its manufacture, regardless of type, although some of the compounds used are sensitizers and many are primary skin irritants. Since it is processed in much the same way as natural rubber, dermatitis may arise from the accelerators, antioxidants, and other compounds. Some dermatitis from synthetic rubbers has already been reported (Schwartz and Peck¹⁵³).

In connection with rubber, sensitivity to gum must be mentioned. Gum is the semi-transparent viscid vegetable substance that exudes from certain trees and shrubs. Feinberg¹⁵⁴ found that the karaya gum used in a hair-setting preparation can cause a dermatitis of the face and neck. He¹⁵⁵ also reported dermatitis of the fingers due to tragacanth in a hand lotion. Gelfand¹⁵⁶ has reviewed the sources of contact with vegetable gums.

ADHESIVE PLASTER

Adhesive tape contains Pará rubber, resins, waxes, and powders. While skin irritation is quite frequently observed in patients using it, the majority of the reactions are of nonallergic nature, being attributable to mechanical factors such as maceration, friction, and tension. True allergic hypersensitivity is rather rare (Grolnick¹⁵⁷) and in most cases relates to the resins (Fig. 188), with rubber in second place. Keil¹⁵⁸ showed that the etiology of hypersensi-

tiveness to adhesive tape is variable since each of 4 patients reacted on patch testing to different ingredients: (1) a combination of commercial dehydrogenated rosin and Beni Pará rubber, (2) a commercial mixture known as pitch subcompound, (3) Beni Pará rubber, and (4) partially purified abietic acid or some fraction present in the acid.



FIG. 188 ALLERGIC CONTACT DERMATITIS
Due to hypersensitivity to resins in adhesive plaster

SIMPLE CHEMICALS

The foregoing paragraphs have been devoted to substances with complex chemical structures as the causal agents in allergic contact dermatoses. We shall now consider, in alphabetical order, the more important simple chemical substances.

Allergy to aluminum and to chromates was reported by Hall¹⁵⁹. He demonstrated, however, that the majority of instances of so-called "dural poisoning" and "aluminum poisoning" were due to chemical irritation from zinc chromate or from the resin ingredients.

Oppenheim,¹⁶⁰ Urbach,¹⁶¹ and others have described chronic, erythematous, pityriasisform,

¹⁵¹ ANDERSON, C. R. *California & West Med.* 61: 60, 1944, Cor-
respondence, *J. A. M. A.* 123: 584, 1945

¹⁵² SCHWARTZ, L. *J. A. M. A.* 127: 389, 1945

¹⁵³ FEINBERG, S. M., and SCHOENKEMAN, B. B. *WISCONSIN M. J.*
39: 234, 1940.

¹⁵⁴ GROLNICK, M. *J. Allergy* 7: 356, 1936

¹⁵⁵ KEIL, H. *J. Indust. Hyg & Toxicol.* 25: 238, 1945

¹⁵⁹ HALL, A. F. *J. A. M. A.* 125: 179, 1944

¹⁶⁰ OPPENHEIM, M. *Wien klin. Wochschr.* 47: 921, 1934

¹⁶¹ URBACH, E. *Zentralbl. f. Haut u. Geschlechtskr.* 52: 292,
603, 1956.

and eczematous dermatoses attributable to sensitization to arsenic. This chemical was contained in the wallpaper paint, colored wood stain, or insecticides with which the patients came into contact (Fig 189). The hypersensitivity may best be determined by patch tests with inorganic and organic trivalent and pentavalent arsenic preparations (e.g., 5 per cent sodium ortho arsenite, sodium metarsenate, neovirsphenamine and stovarsol).



FIG 189 ALLERGIC CONTACT DERMATITIS IN GARDENER
Due to arsenic compound in insect spray

Chlorine vapors released during the process of soldering can provoke genuine allergic dermatitis (Urbach¹⁵⁴⁷). Javelle water (eau de Javelle), a solution of sodium hypochlorite to which potassium dichromate is added as stabilizer, is chiefly responsible for dermatitis in laundresses in France, owing to hypersensitivity to chlorine and/or chromium (Rabeau and Ukrainczyk¹⁵⁴⁸). Since some chlorine is added to the water in most cities in the United States, the possibility must always be borne in mind that these traces of chlorine may maintain the

skin manifestations in individuals hypersensitive to chlorine.

Hypersensitivity to chromium expressed by dermatitis is not infrequently observed in workers in chromium finishing plants in photographers, furriers and others. Hercus and Purves¹⁵⁴⁹ reported pertinent cases in which they were able to demonstrate epidermal hypersensitivity to 0.000003 Gm of chromium.

Metallic cobalt can cause dermatitis in workers in plants manufacturing cemented carbides (Schwartz et al¹⁵⁵⁰). Chiefly affected are points of friction, as well as the neck and eyelids, although the eruption may become generalized.

Formalin is very frequently the cause of severe dermatitis in physicians and laboratory workers. The regular use of formalin containing soap solutions is therefore inadvisable. Moreover, allergy to formalin or to phenol can readily be brought on by plastics made of formalin and carboic acid, as used in the manufacture of umbrella handles, cigarette holders, and numerous other articles. Other common sources of exposure to formalin include medications, such as hexamethylene tetramine, antiperspirants, sterilizing procedures for cabinets, gloves, and instruments, paper towels, tissues, and toilet paper, disinfectants used in shoes, pathologists' fixing solutions, and rubber accelerators.

Biederman¹⁵⁵¹ described contact dermatitis due to ethyl gasoline. It is noteworthy that it was not necessary for the gasoline to come into direct contact with the skin; the vapors per se produced itching and redness, followed by blisters at the exposed sites. However, in such cases hypersensitivity to tetraethyl lead must be ruled out, since several instances of this allergy have been reported.^{1552, 1553}

Germicides of various composition frequently act as contactants, as will be noted throughout this section. Recent reports involving commercial preparations of unknown formula imphicate "Microlene" used in dishwashing machines and contacted only indirectly in handling the dry dishes after several rinsings or

¹⁵⁴⁹ HERCUS C E and PURVES H D. *Lancet* 1: 985, 1933.

¹⁵⁵⁰ SCHWARTZ L, PECK S N, BLAIR K E and MARLSON A. *E J Allergy* 16: 51, 1945.

¹⁵⁵¹ BIEDERMAN J B. *J A M A* 106: 2236, 1936.

¹⁵⁵² JOHNSON D W. *Arch Dermat & Syph* 28: 174, 1933.

¹⁵⁵³ QUERIES and MISCELLANEOUS. *J A M A* 113: 8, 9, 1939.

¹⁵⁴⁷ Idem. *Dermat Ztschr* 54: 92, 1928.

¹⁵⁴⁸ RABEAU H and UKRAINCZYK F. *Ann de dermat et syph* 19: 636, 1939.

merely being in the room with the vapors (Sterling¹⁵⁵¹); "Perm-Aseptic" incorporated in diaper rinses by the diaper services to prevent destruction of textiles by bacteria, mold, and mildew, and resisting boiling and washing (Dobes¹⁵⁵²), and "Germotox" (Vaisberg²⁶⁷³)



FIG 190 ALLERGIC CONTACT DERMATITIS

Due to bichloride of mercury remaining on thermometer used for axillary temperatures

Hypersensitiveness to *lysol* is quite commonly observed, not only in individuals using the chemical to disinfect foot baths, toilet bowls, and other articles, but also in women who use it in vaginal douches.

Mercury is a particularly potent skin sensitizer. When bichloride of mercury was widely used as a disinfectant, cutaneous manifestations from this source were often seen. The localization of the latter not infrequently di-

rected suspicion toward the possibility of a mercury hypersensitiveness. Thus, involvement of the axilla (FIG. 190) suggests the use of thermometers disinfected with mercuric chloride; of the buttocks, contact with a toilet seat cleansed with the same chemical. Workers employed in mercury mines often exhibit specific cutaneous symptoms. The organic mercurial antiseptics are potent epidermal allergens. A pertinent instance of contact dermatitis due to tincture of merthiolate was reported by Hollander.¹⁵⁵⁶ Other examples of sensitivity to mercurial compounds will be found earlier in this chapter.

Nickel dermatitis is frequently observed in workers in the nickel industry. The lesions are located chiefly on the exposed areas, including the mucosa, such as the conjunctivae. Nickel hypersensitiveness caused by coins has also been reported (FIG. 191), with localization of the lesions primarily on the fingers, though also on the thighs (due to coins in pockets). Some cases continue to have lesions of their hands as long as they put their hands in the pockets which previously contained coins. The literature mentions sensitization brought on by spectacle rims, wrist watches, garters, and zippers—also by a nickel-plated tonsil snare on the fingers of a physician (Wise and Sulzberger¹⁵⁵⁷) and by nickel-plated instruments on the hands of a dentist (Stokes¹⁵⁵⁸). Other sources of contact are handbag clasps, belt buckles, hooks, hairpins, certain types of "jewelry," and household objects.

Paradichlorobenzene, used as a moth preventive, is often the cause of severe dermatitides.

Persulfates are added to flour for bleaching purposes and also to make the flour bake more readily. Investigations during the past few years have disclosed that ammonium and potassium persulfate are the main causes of the characteristic baker's and miller's dermatitis. The lesions are located chiefly on the hands and forearms (FIG. 192), but the entire skin surface is sometimes involved. Baird¹⁵⁵⁹ reported a case of allergic contact dermatitis of exposed areas due to infinitesimal traces of

¹⁵⁵⁶ HOLLANDER, L. Arch. Dermat. & Syph. 50: 123, 1944

¹⁵⁵⁷ WISE, F., and SULZBERGER, M. B. Jr. Bk. Dermat. & Syph., 1934

¹⁵⁵⁸ STOKES, J. H. personal communication.

¹⁵⁵⁹ BAIRD, K. A. J. Allergy 16: 195, 1945

¹⁵⁵¹ STERLING, A. Ibid. 127: 219, 1945

¹⁵⁵² DOBES, W. L. Ibid. 128: 281, 1945

another flour "improver," benzoyl peroxide or rather its residue, benzoic acid. It would be erroneous, however, to attribute all such conditions to the chemicals, for many of these pa-

tients were attributable only to hypersensitivity to the persulfate while the concurrent rhinopathy was found to be due to allergy to flour.



FIG 191 POSITIVE REACTIONS TO PATCH TEST WITH NICKEL CONTAINING SILVER COINS

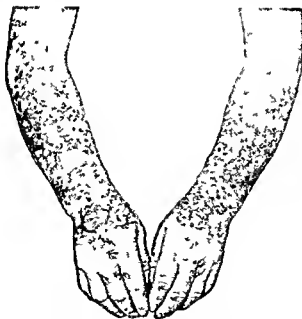


FIG 192 ALLERGIC CONTACT DERMATITIS IN BAKER
Due to ammonium persulfate used as flour bleach

tients are demonstrably hypersensitive only to flour itself, while a third group is allergic both to the flour and to the added ingredients (Dischoeck and Roux⁴¹⁷). Finally, the senior author has described a case in which skin manifesta-

Contact dermatitis due to *petroleum* has been observed, even after a single brief contact (Rosenbaum¹⁵⁶⁰) although it is relatively rare

⁴¹⁷ ROSENBAUM, M. G. Arch. Dermat. & Syph. 48: 193, 1943



FIG. 193. ALLERGIC CONTACT DERMATITIS IN HOUSEWIFE, DUE TO SOAP
Positive patch test with 1 per cent solution of soap

despite the magnitude of the oil industry and the widespread use of this substance. It is characterized by a canary yellow color of the bullae. This condition must be differentiated from other well recognized petroleum dermatoses not on an allergic basis.

Quite commonly encountered are cases of hypersensitiveness of the skin to *phenol*, in the form of carbolic acid, cresol, and other derivatives, as well as to synthetic plastics made of phenol, and used in ornamental knobs of walking canes, in penholders, fancy boxes, and other items.

Soaps are more often primary irritants than true allergens. A full discussion of the importance of soaps in toxic contact dermatitis will be found in the relevant section (p. 695). Soap represents a sodium or potassium salt of the higher fatty acids containing 8 or more carbon atoms. The latter are derived from various vegetable and animal fats. The former include linseed oil, cottonseed oil, corn oil, coconut oil, rapeseed oil, olive oil, palm oil, sunflower oil, sesame oil, tung oil, and kapok oil. The animal fats are rendered from packing house waste and garbage. In addition, soaps may contain such chemicals as sodium or potassium hydroxides, sodium carbonate or silicate, di- or trisodium phosphates. The principal mechanisms by which soap produces cutaneous



FIG. 194 ALLERGIC CONTACT DERMATITIS IN HOUSEWIFE, DUE TO TURPENTINE

affections are the alkali and the fatty-acid effects, together with detergent and removal effects (Sulzberger and Baer¹⁴¹). Neverthe-

¹⁴¹ SULZBERGER, M. B., and BAER, R. L. in *Medical Uses of Soap*, edited by Fishbein, M. Philadelphia: Lippincott, 1945.

less, in a few cases, specific allergic sensitivity to the dyes, fillers, fats, fatty acids, and other ingredients can be demonstrated. In these cases, a true allergic contact dermatitis may follow even a single exposure to the soap. Soaps are to be considered as allergenic agents only when a 1 or 2 per cent solution will evoke a skin reaction on patch testing (Fig 193). A recent review by Brown¹⁸⁴² reveals the fact that soap sensitivity is an extremely complex phenomenon. Among other factors, the physiologic condition of the skin, its allergic potentialities, the presence of concomitant disease, and the degree of exposure must be considered. The evaluation of a positive patch test reaction to soap is therefore difficult, and the test itself is rarely dependable. There is usually a more intense response to tests with soap solutions than with undiluted soap (Sulzberger and Baer¹⁸⁴¹), although liquid soaps should be used without dilution. Moreover, the hypersensitivity may be a reaction to the drugs or other added ingredients, such as sulfur, tar, creosote, glycerin, or perfumes, and therefore skin tests with these substances should be carried out in pertinent cases. Finally, soap contained in steel wool scouring pads (Brillo) may be responsible for dermatitis in housewives and domestics. Sulfonated oil detergents recommended as soap substitutes apparently give rise to little or no sensitization (Lane and Blank¹⁸⁴³).

Turpentine is known to elicit allergic dermatides in artists, house painters, and workers engaged in lacquering, varnishing, polishing, and printing, as well as in housewives and domestic servants handling soaps containing

turpentine, and shoe polish and floor waxing preparations (Fig 194). The hypersensitivity is sometimes of such extreme degree that severe manifestations are elicited when the patient merely enters a room in which the floor had recently been waxed. In cases in which the dermatitis is due to a turpentine substitute, it is important to perform the skin tests with this substance, since sometimes the hypersensitivity will not be directed to turpentine simultaneously (Schmidt¹⁸⁴⁴).

Zinc, either as the metal or as one of its salts, usually the chloride, may very rarely cause a dermatitis in persons occupationally exposed, particularly welders (Freeman¹⁸⁴⁵).

F DUST

Stroud¹⁸⁴⁶ showed that the oil extracted from house dust produced positive patch test reactions in certain patients with allergic contact dermatitis. The senior author has observed 2 cases in which dust seemed to be the most important cause of a widespread dermatitis. This conclusion was based on the positive epidermal responses to autogenous dust and the good results obtained by dustproofing the environment of the patients.

While only two instances can be cited in support of the theory that dust can act as a contactant, it seems advisable to keep this possibility in mind in cases of contact dermatitis of obscure origin.

As shown in our earlier discussion (p 236), house dust is a highly complex substance and may differ considerably from place to place. Hence testing with stock house dust may be without value.

¹⁸⁴² BROWN E A. *Ann Allergy* 3: 50, 1945.

¹⁸⁴³ LANE C G and BLANK I H. In *Medical Uses of Soap*, edited by Fishbein M. Philadelphia: Lippincott, 1945.

¹⁸⁴⁴ SCHMIDT W. *Dermat Wehnschr* 117: 389, 1941.

¹⁸⁴⁵ FREEMAN H E. *J A M A* 119: 1015, 1942.

¹⁸⁴⁶ STROUD C M. *J Allergy* 6: 464, 1933.

CHAPTER XVII

PHYSICAL AGENTS

FOR didactic and therapeutic purposes, physical hypersensitiveness is subdivided according to the etiologic agents involved. The methods of testing for the various physical agents are described on page 180

Duke¹⁵⁶⁷ introduced the term "physical allergy" to indicate an altered reactivity to physical agents such as mechanical irritation, cold, heat, light, or mental and physical effort, without implying an allergic (antigen-antibody) mechanism. He distinguished two types: the contact type in which reaction is confined to the area directly affected by the physical agent, causing, for example, a localized urticaria, and the reflex type, in which the reaction occurs not only at the site of contact but also in distant structures, and sometimes in distant structures only (generalized urticaria, tachycardia). He considered the contact type as comparable to the drug allergies, while the reflex type was regarded as probably caused by a disturbance of the heat-regulating mechanism of the body, although others have suggested that histamine-like effects are responsible.

Since Duke first called attention to physical agents as the causes of a few cases of urticaria and angioneurotic edema, and sometimes also of such conditions as asthma, coryza, headaches, and tachycardia, an extensive literature on the pathogenesis of physical allergy has appeared. Quite a few authors have adduced all the evidence necessary to demonstrate the allergic nature of their cases. On the other hand, many have never succeeded in performing passive transfer of this type of hypersensitiveness.

A. PATHOMECHANISM OF PHYSICAL HYPERSENSITIVENESS

On the basis of the pertinent literature and of our findings (80 cases studied during the past twenty years and in part previously reported^{1568, 1569}), hypersensitiveness to physical

agents can be based on one of the following mechanisms:

1. PRIMARY PHYSICAL ALLERGY

Physical agents such as cold, heat, light, pressure, and mechanical stimuli can become operative on the basis of specific antigen-antibody reactions. Nevertheless, we must warn against the assumption that allergy in the strict sense is a frequent cause of these conditions. A review of the literature by Rajka¹⁵⁶⁹ revealed only 36 cases in which passive transfer of physical hypersensitiveness was successful. To these should be added cases of sensitivity to mechanical stimuli reported by Duke¹⁵⁷⁰ and the senior author.¹⁵⁵ On the other hand, in many published and unpublished instances, attempts at passive transfer on the part of numerous investigators, including the writers, were unsuccessful. These negative results, in conjunction with the facts presented in subsection 4 below, indicate that many cases of physical hypersensitiveness are pathergic rather than allergic in nature.

2. SECONDARY PHYSICAL ALLERGY

Manifestations of this group may also be considered as allergies, but allergies to substances produced by the action of physical agents in the patient's own skin, mucous membranes, or muscles. These substances, which we consider as autogenous antigens, result from some chemical or physico-chemical alteration of the proteins of the tissues; they become foreign to the organism and thus assume the nature of antigens. Bronfenbrenner¹⁵⁷¹ expresses agreement with this viewpoint. He points out that since exposure to nonantigenic chemical stimuli has been shown to result in the *in vivo* union of the chemicals with the products of the injured tissue, with the consequent formation of an antigenic product, it is not inconceivable that injury by physical means may so change the tissue as to impart to

¹⁵⁶⁷ DUKE, W. W. *J. A. M. A.* 84: 736, 1925

¹⁵⁶⁸ URBACH, E., and FASAL, P.: *Wien klin Wchnschr.* 46: 1069, 1933

¹⁵⁶⁹ RAJKA, E. *J. Allergy* 13: 327, 1942

¹⁵⁷⁰ DUKE, W. W. *ibid* 6: 568, 1935.

¹⁵⁷¹ BRONFENBRENNER, J. *J. Allergy* 14: 105, 1943

it a new specificity and thus render it auto antigenic. The experiments of Karady (p 135) serve as an example. In a similar manner, plunging into cold water, with consequent sudden cooling of large portions of the body, can cause the production of these autogenous antigens. This might well explain many of the not uncommon deaths or severe anaphylactic manifestations occurring in bathers.

Furthermore, previous bacterial infections can also make possible the production of such autogenous antigens. Thus, Burky⁵⁶ made the following important demonstration. Rats were prepared with staphylococcus toxin, cultured in a broth made from rat muscle tissue. These rats then reacted anaphylactically to trauma or, more precisely, to substances released in their own tissues by the trauma.

3 HISTAMINE EFFECT

The future will have to decide whether the basic mechanism is allergic or pathergic in those cases of hypersensitiveness in which the effects of a specific physical agent release a histamine-like substance in the tissues—in short, whether or not there is an antigen antibody reaction. We are personally inclined to include these conditions among the pathergies. Our assumption finds support in cases in which use of a tourniquet on an extremity confines locally the urticarial manifestations produced by subsequent application of physical agents. The release of the pressure is followed by a generalized skin reaction (Horton and Brown,¹⁵⁷² Lehner¹⁵⁷³). Further confirmation is found in the experiments of Lewis and Grant¹⁵⁷⁴. They collected blood serum from cases of physical allergy after exposing both arms to the influence of the specific physical agent and applying a tourniquet to only one. The serum from the bound arm elicited a decidedly stronger urticarial reaction, both in the patient and in a normal control subject, than did the serum from the other arm. Urbach and Fasal¹⁵⁶⁸ showed that the cantharides blister content from a skin area made specifically urticarial by pressure was definitely more irritating to the skin than blister content from a normal skin area of the same patient.

The presence of a histamine like substance in these cases seems to be indicated by the findings of Horton, Brown, and Roth¹⁵⁷⁵. They demonstrated that the systemic reactions (e.g. behavior of blood pressure, pulse rate and gastric acidity) following exposure to cold in cases of hypersusceptibility to cold are comparable in every way to the symptoms in persons who have received injections of histamine hydrochloride. The histamine theory received further support in the therapeutic success achieved by Roth and Horton¹⁵⁷¹ with histaminase, and by Bray,¹⁵⁸⁰ Saylor and Wright,¹⁵⁷⁶ and others with histamine injections.

4 VASONEUROPATHY

The following observations lead us to assume that instability of the central or peripheral vasomotor mechanism may be responsible for the abnormal neurovascular response to local physical agents in some cases. These observations are (a) both cold and hot baths can cause urticaria (Hopkins, Kesten, and Hazel¹⁵⁷⁷), (b) urticaria can be restricted to certain parts of the body (Musger Urbach), (c) in certain cases manifestations are not elicited by every type of exposure to cold but only by cold water, or only by cold air (Biberstein Klein), (d) as reported by Duke,¹⁵⁶⁷ certain individuals react to cold only when they have just recently been exposed to heat, or vice versa—i.e., the reaction is elicited by sudden change in temperature and not by the degree of temperature itself, (e) cases of cold hypersensitiveness have been cured by the elimination of focal infection (Kerl,¹⁵⁷⁸ Urbach¹⁵⁷⁹), of parasitic infestation (Kerl¹⁵⁷⁸), of hypo acidity (Rahier), of hypothyroidism (Crehange), (f) as first described by Duke, cold urticaria can be prevented by local application of heat, and heat urticaria by application of cold, (g) as in a case reported by Urbach, Herrman, and Gottlieb,¹⁵⁷⁰ the symptoms of vasoconstriction are followed after a while by those of general vasodilation, (h) in the cases of Kile and Rusk,¹⁵⁸⁹ as well as that just

¹⁵⁷² HORTON B. T. and BROWN G. E. *Am J M Sc* 18 191 1929
197 1263 1936

¹⁵⁷³ SALLER L. and WRIGHT I. *Am J M Sc* 192 388 1936

¹⁵⁷⁴ HOPKINS J. G. KESTEN B. M. and HAZEL O. G. *Arch Dermat & Syph* 38 679 1938

¹⁵⁷⁵ KERL W. *Dermat Wchnschr* 95 1253 1932

¹⁵⁷⁶ URRACK E. *Zentralbl f. Haut u. Geschlechtskr* 50 646 1935

¹⁵⁷⁷ KILE R. L. and RUSE H. A. *J A M A* 114 1057 1940

¹⁵⁷⁸ HORTON B. T. and BROWN G. E. *Am J M Sc* 18 191 1929

¹⁵⁷⁹ LEHNER E. *Klin Wchnschr* 8 306 1929

¹⁵⁸⁰ LEWIS T. and GRANT R. T. *Heart* 11 209 1924

cited,⁵⁷⁰ the cold hypersensitiveness began at birth, and about 50 per cent of all relatives in several generations were affected.

In our opinion all these facts support our concept that many of these cases are due to functional disturbances in the vascular innervation, or, as we have termed it elsewhere,¹⁵⁶³ "cold-specific vasomotor neuropathy." We now prefer the simpler designation "cold pathergy."

5. DISTURBANCES OF THE TEMPERATURE-REGULATING MECHANISM

It is to be assumed that central disturbances of the temperature-regulating mechanism are the causes of certain pathologic reactions in the blood vessels of the skin. These derangements are attributable to preceding infectious diseases, febrile diseases, certain generalized skin diseases, intracranial disorders, and the like. Duke⁵⁶⁷ favors this concept as an explanation for what he terms the "reflex-like" type of physical allergy. Such central disturbances may perhaps be responsible for the general symptoms, which are sometimes very severe. It is known that merely dipping the hand into cold water occasionally brings on pallor, tachycardia, nausea, spasm of the retinal arteries (writers' case), and fainting spells. It is possible that the cases of death while bathing described by Horton and others, may belong to this group.

B. COLD

If the physician engaged in experimental study of patients with urticaria always bears in mind the possibility that "cold" may be the causative factor, and if he performs the tests described on page 180, he may be surprised to find that the incidence of so-called cold urticaria is relatively high. This condition may be either localized or generalized. In the former case, the urticarial manifestations are restricted to the site of direct exposure to cold; in the latter, there is likely to be a widespread urticarial response, even to temperatures of 5 to 10 degrees above zero centigrade (41 to 50 F.). It is to be noted, furthermore, that when the condition is generalized, the hypersensitiveness is by no means restricted to the skin, but may also involve the mucosa. In this connection, the observations of Duke⁵⁶⁷ are

especially interesting: after drinking a glass of cold water, his patient complained of pains in the mouth, esophagus, and stomach—while exposure to cold air brought on swelling of the lips and tongue, as well as lacrimation, coughing, and even general collapse-like reactions when the exposure was prolonged. Cases of nasal congestion and obstruction, cough, and even asthma due to the inhalation of cold air, and particularly cold damp air, are not uncommon. We exclude from consideration here those patients who are simultaneously sensitive to inhalants and foods and in whom the change of temperature acts merely as a nonspecific pathergic stimulus. Affolter¹⁵⁹⁷ described a case in which cold water on the skin brought on itching, erythema, urticaria, headache, a general feeling of weakness, profuse diarrhea, and collapse, Schlenker, a case with anaphylaxis and an alarming edema of the glottis; Wilder, pruritus, generalized erythema of the skin, visual disturbances, and spells of fainting.

Mention must be made here of a rarely encountered clinical picture—late urticaria due to cold—first described by Freund¹⁵⁹¹. In this condition the symptoms first appear twenty-four to forty-eight hours after the exposure to cold and only on the exposed areas.

Peters and Horton,¹⁵⁵² as well as Yater and Nicklas,¹⁵⁵⁸ have reported association of cold urticaria with purpura of the affected parts. Harris et al.¹⁵⁵⁴ observed hemoglobinuria in 3 cases of cold urticaria.

Ever since Horton¹⁵⁵³ pointed out that cold anaphylaxis could be the cause of death while bathing, the subject has attracted considerable attention in the literature. The writers have themselves observed a number of instances in which the sudden onset of cold urticaria rendered bathers so helpless that they could hardly be rescued from drowning. The entire skin of these individuals presented one huge urticarial swelling. Their loss of consciousness can probably be explained on the basis of a cerebral

¹⁵⁶¹ FREUND, E. *Ztschr. f. physik. Therap.* 32: 163, 1926.

¹⁵⁶² PETERS, G. A., and HORTON, B. T. *Proc. Staff Meet., Mayo Clin.* 15: 631, 1941.

¹⁵⁶³ YATER, W. M., and NICKLAS, E. W. *Ann. Int. Med.* 15: 143, 1941.

¹⁵⁶⁴ HARRIS, K. E., LEWIS, T., and VAUGHAN, J. M. *Heart* 14: 301, 1929.

¹⁵⁶⁵ HORTON, B. T. *Proc. Staff Meet., Mayo Clin.* 2: 276, 1927.

edema, resulting from the same mechanism as their temporary loss of vision

Andes¹⁵⁸⁶ holds that allergy to physical factors, such as chilling drafts (on face head back of neck, or whole body), especially when relaxed (during sleep) or perspiring swimming and diving, atmospheric conditions, and abrupt changes in temperature, as well as exposure to sunlight and irradiation, may be responsible for noninfectious disease of the paranasal sinuses. He attributes the changes to a localized urticaria like reaction in the nasal tissues

Williams¹⁵⁸⁷ suggests that myalgia of the head, affecting such muscles as the trapezius, sternocleidomastoid, temporalis, occipitofrontalis, and the pharyngeal muscles, is due to physical allergy precipitated by exposure to drafts, changes in temperature, changes in atmospheric pressure with approaching storms, emotional stimuli, and anxiety states. This condition is readily confused with psychogenic headaches, migraine, glossopharyngeal neuralgia, and primary and secondary fibrositis, but differentiation is necessary for rational therapy. Other myalgias may well be of similar origin. Although this latter question has not as yet been definitely decided, the investigations by Freund¹⁵⁹¹ certainly favor the idea of such a possibility, at least in some cases

Other disorders thought possibly to be due to cold allergy in some cases include nausea and vomiting, diarrhea, irritable bladder, functional cardiac disorders, tremor, hyperesthesia to cold, arthralgias, and vertigo

Whether the pathogenesis is allergic or pathergic must be determined by appropriate experimental investigation of each case. In 19 cases it was possible to demonstrate the presence of an antigen antibody reaction by means of passive transfer tests (Lehner,¹⁵⁷³ 1588; Lieberman,¹⁵⁸⁹ Harris et al.¹⁵⁸⁴ Covisa and Prieto¹⁵⁹⁰ Bernstein,¹⁵⁹¹ Weissenbach and Brisset¹⁵⁹² Affolter,¹⁵⁹³ Benjamins,¹⁵⁹⁴ Bodenstein,¹⁵⁹⁵ Per nyes Pietsch¹⁵⁹⁶)

The relationship of untoward reactions from cold to the activation of pre existing 'cold' iso hemagglutinins with resultant agglutination and hemolysis has never been adequately studied. There is suggestive evidence that this mechanism may be operative in some cases. Further investigation of this problem promises to be fruitful

In other cases cold allergy may be due to a metallergic mechanism. Thus Urbach and Greenberg¹⁵⁹⁷ reported on a patient in whom local urticarial reactions to the application of cold appeared only when he was in a nutritional allergic state. This patient first developed hives after eating sausage containing pork blood, it was noted that a wheal response to cold water occurred only during such an attack. This sequence of events may be explained as follows: the physical agent—cold—here acted as a hapten which, after conjugation with the carrier substance (in this case, the ingested pork blood) formed a complete antigen that evoked the urticaria

Aside from the fact that passive transfer of hypersensitiveness to cold is often unsuccessful, there are several other pertinent clinical points that serve as a warning against hastily assuming that every case of this kind is of allergic origin. For, on the strength of numerous observations (see p. 410 for literature), many cases would seem to be based on vasoneurosis, an abnormal reactivity of the vaso motor mechanism belonging to the group of nonallergic pathergies. Thus, some reports describe cases in which both hot and cold baths produce urticaria, cases in which it appears only on certain—though sometimes rather large—areas, cases in which hives are produced not by every kind of exposure to cold, but only by cold air or only by cold water. Further more, the literature includes highly significant cases in which the hypersensitiveness to cold has been totally and often abruptly cured by the successful treatment of focal infections and infestations, of disturbances of gastro intestinal absorption, of hypo acidity, or of endocrine dysfunction (e.g., hyperthyroidism, menstrual

¹⁵⁸⁶ ANDRES J. E. *Journal Lancet* 40: 384 1944

¹⁵⁸⁷ WILLIAMS H. L. *Proc. Staff Meet. Mayo Clin.* 20: 177 1945

¹⁵⁸⁸ LEHNER E. *Zentralbl. f. Haut u. Geschlechtskr.* 41: 199 1932

¹⁵⁸⁹ LIEBERMAN E. *ibid.* 34: 406 1930

¹⁵⁹⁰ COVISA J. S. and PRIETO J. G. *Dermat. Wochenschr.* 91: 1188 1930

¹⁵⁹¹ BERNSTEIN F. *Dermat. Ztschr.* 64: 212 1932

¹⁵⁹² WEISSENBACH R. J. and BRISSET J. P. *Ann. de med.* 32: 333 1932

¹⁵⁹³ AFFOLTER J. *Schweiz. med. Wochenschr.* 63: 581 1933

¹⁵⁹⁴ BENJAMINS C. E. *Nederl. tijdschr. v. geneesk.* 78: 5362 1934

¹⁵⁹⁵ BODENSTEIN E. *Zentralbl. f. Haut u. Geschlechtskr.* 52: 361 1936

¹⁵⁹⁶ PERNYES PIETSCH S. *ibid.* 56: 8 1937

¹⁵⁹⁷ URBACH E. and GREENBERG S. *Arch. Dermat. & Syph.* 39: 987 1939

irregularities). Even psychosomatic factors may be the predisposing element, as convincingly illustrated by Abramson's¹⁴⁹³ case. A woman who was depressed by the news of the death of intimate friends developed giant hives on contact with cold water. After the patient had readjusted mentally, the whealing response to cold disappeared. That many an instance is not of allergic origin is further indicated by the fact, first reported by Duke, that cold urticaria can not infrequently be relieved and sometimes even cured by the application of heat, and that application of cold can similarly benefit urticaria due to heat.

young man who evidenced from birth a specific hypersensitiveness to cold air, but not to the applications of other forms of cold. Of the twenty-eight members of his family (four generations), sixteen others showed the same type of hypersensitiveness, also beginning at birth (FIG. 195). After this report was published, the patient married and had a child that exhibited the same manifestations from the very day of birth. It is particularly noteworthy that only those areas normally exposed to the air (e.g., face, hands, legs) gave reactions (FIGS. 196, 197, 198). These consisted of local urticaria and diffuse swelling, as well as certain

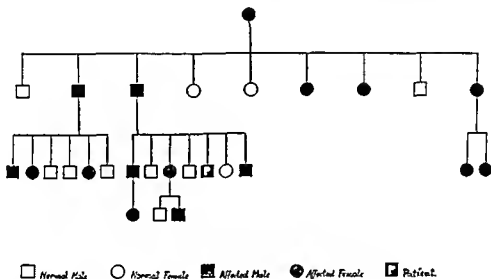


FIG. 195. GENEALOGIC CHART SHOWING 17 CASES OF HYPERSENSITIVENESS TO COLD IN FOUR GENERATIONS

Lehner and Rajka have advanced the claim that cold as well as heat urticaria can be cured by the systematic application of cold and heat respectively. In our opinion, however, this procedure is not necessarily to be regarded as a specific desensitization measure. Nor does its effectiveness necessarily serve as a confirmation of the allergic character of the condition. In view of the fact that the therapeutic effect is here achieved by gradual intensification of the homologous temperature, the procedure might very well be one of habituation in the non-allergic sense.

An example of the pathergic type of cold hypersensitiveness is afforded in the case reported by Urbach, Herrman, and Gottlieb,⁵⁷⁰ of a

other symptoms that can be explained only as the result of vascular constriction (piercing pains, followed by numbness and extreme "whiteness"). This vascular constriction was followed by a general vasodilatation resulting in a temperature as high as 101 F., a feeling of being overheated, perspiration, and drowsiness. These facts all speak against the existence in this case of an underlying cold allergy on the basis of an antigen-antibody reaction. On the contrary, they point to a specific hypersensitiveness of the peripheral neurovascular system to cold air, i.e., "cold pathergy." A quite similar observation of familial hypersensitiveness to cold, affecting about 50 per cent of all relatives in several generations, and beginning at birth, had previously been reported by Kile and Rusk.¹⁵³⁰

¹⁴⁹³ ABRAMSON, H. A. *Psychosom Med* 3: 435, 1941

The treatment of hypersensitiveness to cold is by no means an easy matter. If the history and studies in a case point to an infection in festation, endocrine dysfunction or gastro

calcibronat are recommended. These injections are to be given daily for about one week together with phenobarbital orally ($\frac{1}{8}$ to $\frac{1}{2}$ gram three times a day). Preliminary obser



FIG 196 COLD PATHERGY URTICARIAL LESIONS OF FACE
Appearing after thirty five minutes in cold room (temperature 10 F)

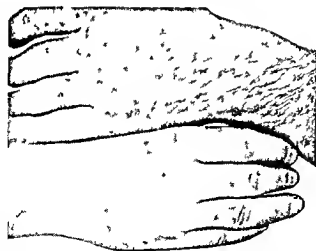


FIG 197 COLD PATHERGY URTICARIAL LESIONS ON
LEFT HAND

Appearing after thirty five minutes in cold room (temperature 10 F). Right hand had been kept gloved. Same patient as in Figs 196-198.

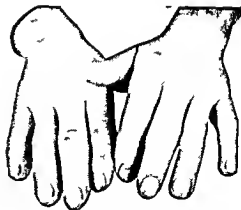


FIG 198 COLD PATHERGY SWELLING OF LEFT HAND

Appearing about thirty minutes after leaving cold room. Right hand had been kept gloved. Same patient as in Figs 196-197.

intestinal disturbance as the underlying cause appropriate therapeutic measures must be instituted. Otherwise massive intravenous injections of calcium gluconate or preferably

variations by Fernberg and Friedlaender.⁶⁸² Pillsbury²⁷⁸⁷ and the senior author indicate that a new synthetic histamine antagonist benadryl (β -dimethylaminoethyl benzhydrol ether hy

drochloride) in doses of 50 to 100 mg. three times daily is effective in cold urticaria, and by Williams,^{41c} in the treatment of the syndrome of physical allergy of the head. Williams⁴³⁷ has also advocated niacin, beginning with 25 mg. hypodermically and increasing by a like amount daily until relief is obtained, usually at a level of about 100 mg. twice daily. After 2 or 3 months, 100 mg. of niacin by mouth three times a week is generally sufficient. If these treatments do not seem to help, histamine-azoprotein may be tried very cautiously in an effort to render the patient immunologically tolerant of histamine, or a course of histamine therapy may be given on the theory that it will eventually exhaust the reactive capacity of the shock organ. Horton and Roth recommended injections of histamine twice daily for two or three weeks, in doses of 0.1 mg. or less. These authors also advocate a trial with histaminase (5 to 10 units orally, three times a day). The present writers have had rather encouraging results with oral histamine therapy. The patient takes 1 drop of histamine dihydrochloride 1:1,000 dissolved in 20 per cent alcohol in one-half glass of water three times a day before meals, increasing the dose by one drop each day until clinical improvement is attained. If focal or systemic reactions ensue, as occurs not too rarely, the dosage is reduced or a 1:10,000 solution given. This therapy should be continued for about four to eight weeks.

Finally, Horton and Roth, as well as Lehner and Rajka, advise "autodesensitization" by means of immersion of the patient's hand or foot in water at 17 C. (65 F.) for one or two minutes twice daily, with the temperature of the water being gradually and slowly reduced, over a period of three to four weeks, to a minimum of 7 C. (45 F.). Others have suggested contrast baths, such as alternating hot and cold showers, or rubbing an increasing area of the body surface with ice for a few minutes daily. If reactions occur during treatment, they may be controlled by the application of heat.

C. HEAT

Everything that has been said concerning cold allergy—and pathergy—applies to the states of hypersensitiveness brought on by

heat (FIG. 199), or by overheating resulting from physical exertion (FIG. 200) such as exercise (Ormsby¹⁴⁹⁹), perspiring, eating too rapidly (tachyphagia—Pagniez and de Gennes¹⁶⁰⁰), as well as by mental overexertion, fatigue (Joltrain), and psychic stimuli (Hopkins and associates¹⁸⁷⁷). Patients presenting the "effort syndrome" are often found to be sensitive to heat.

It is especially noteworthy in this connection that many a case diagnosed as "cold allergy" is in fact not due to cold at all, but to the flush of heat following the exposure to cold.

It is also well to remember that occasionally patients with heat hypersensitiveness who are also affected by sunlight, are not light-hypersensitive in the true meaning of the term, but merely react to the radiant heat of the sunlight. Thus, the senior author observed a boy who, during three consecutive summers—and only during the summers—had suffered urticaria, abdominal cramps and diarrhea following sun baths. The patient presented a heat hypersensitiveness of high degree, manifesting reactions after relatively insignificant exertion. During the cooler seasons, his symptoms had always spontaneously disappeared.

The clinical symptoms commonly observed in heat hypersensitiveness may be divided into (1) contact urticaria, and (2) general symptoms, brought on by "reflex" mechanisms, and including generalized urticarial eruptions, extrasystoles, tachycardia (Duke¹⁶⁰¹), asthma (Swineford, Jr., and Weinberg¹⁶⁰²), migraine (Luckner and Mann¹⁶⁰³), and syncope (Vaughan²⁴). The pathogenesis seems to vary in different cases. Lehner and Rajka¹⁶⁰⁴ and Richter¹⁶⁰⁵ succeeded in demonstrating a true allergic mechanism by means of the Prausnitz-Kuestner method of passive transfer, and Melzer and Wlassics,⁶² in 2 cases, with the Urbach-Koenigstein technic. In many other instances the assumption of an underlying allergy appears to be highly problematic. The allergic character of the condition certainly seems to be

¹⁴⁹⁹ ORMSBY, O. S. *Arch. Dermat. & Syph.* 27:171, 1933

¹⁶⁰⁰ PAGNIEZ, P., and GENNES, L. de. *Bull. et mem. Soc. med. d. hop. de Paris* 45: 577, 1921

¹⁶⁰¹ DUKE, W. W. *J. Allergy* 4 38, 1932

¹⁶⁰² SWINEFORD, O. J., JR., and WEINBERG, H. *ibid.* 4: 530, 1933

¹⁶⁰³ LUCKNER, H., and MANN, E. *Klin. Wchnschr.* 18: 767, 1939

¹⁶⁰⁴ LEHNER, E., and RAJKA, E. *Krankheitsforschung* 8 85, 1930

¹⁶⁰⁵ RICHTER, W. *Dermat. Wchnschr.* 100 129, 1935

especially contradicted by those cases in which the wheal formation is not restricted to the site of exposure to the physical agent but spreads over the entire body (reflex like reaction of Duke). Nor does the assumption of an under

lying urticaria provoked by warming of the body by emotion and exercise—was due to the release of acetylcholine in the skin as the result of centrally or reflexly induced stimulation of the efferent nerve fibers. This resulted in



FIG. 19. HEAT URTICARIA APPEARING AFTER HOT BATH

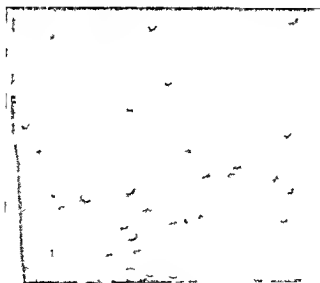


FIG. 20. EFFORT URTICARIA PRODUCED BY STRENUOUS PHYSICAL EXERTION

Note follicular distribution

lying allergy receive any support from those cases in which mental strain or psychic stress brings on urticarial manifestations. Grant and his associates¹⁶⁰⁶ presented experimental evidence that the heat and effort syndrome

turn in the liberation of H substance from the skin cells. Hopkins¹⁷⁷ confirmed Grant's claim that these cases are definitely hypersensitive to acetylcholine.

As for the treatment of heat and effort hypersensitivity, the principles recommended for cold hypersensitivity are worthy

¹⁶⁰⁶ GRANT, R. T., PEARSON, R. S. B. and COMEAU, W. J. *Clin. Sci.* 2: 23, 1936.

of a trial. Vaughan attempted "autodesensitization" by placing the patient's hand in water heated to 37 C. (98 F.) and keeping it there while the temperature was gradually raised to a maximum of 43 C. (110 F.). If this exposure is tolerated, the patient may be given a full hot bath (38 C. or 100 F.). The course of treatment usually lasts from four to six weeks. Cayen¹⁶⁰⁷ reported good results with diathermy administered with gradually rising temperatures, and Swineford and Weinberg¹⁶⁰⁸ with intravenous typhoid therapy.

Lehner and Rajka explained the gradual decrease in the reactivity of the skin to systematic exposure to heat on the theory of the formation of specific substances (dereagins). We are inclined, however, to consider the results of these procedures, at least in most cases, as due to habituation.

Vaisberg¹⁶¹⁷ and Goodson¹⁶¹⁸ obtained promising results from the use of histaminase, as well as of histamine administered in minute and gradually increasing doses. Histamine-azoprotein may be tried.

In cases in which physical exertion and mental overexertion play a part, treatment with carefully graduated physical exercise (at first passive) or mental exertion (beginning with mild, pleasant tasks such as reading or attending theater) should be started as soon as tolerance for heat and muscle strength has been gained. Reactions may be controlled by application of cold.

D. LIGHT

Only a small proportion of cases of light hypersensitiveness are truly allergic in character, while the majority of them, in the writers' opinion, are based on nonallergic pathology.

1. PATHOGENESIS

Successful passive transfer of the hypersensitiveness has to date been reported only by Stein¹⁶⁰⁵ Rajka,^{1609, 1389} Calloway,¹⁶¹⁰ and Epstein¹⁶¹¹ (using blood serum), and by Flarer¹⁶¹² (using blister content). Furthermore, there are a large number of cases in which correction

of a hepatopathy, a gastro-intestinal disease, an endocrine dysfunction, an infection, or an intoxication was followed either by complete cure or at least temporary disappearance of light hypersensitiveness—the improvement presumably being attributable to the fact that the formation of photosensitizing or photodynamic substances was arrested or interrupted.

Thus, in a case of hydroa vacciniforme, Urbach and Bloech¹⁶¹³ brought about an improvement in the patient's syphilitic hepatitis by means of antiluetic therapy, as a result, the concurrent porphyriopathy disappeared. For several months thereafter the patient tolerated long exposures to strong sunlight perfectly, until after a while liver function was again impaired, and the porphyrinemia and light hypersensitiveness reappeared. Barber¹⁶¹⁴ reported the case of a man who, after overindulgence in alcohol, exposed himself to sunlight and acquired light dermatitis. His liver was greatly enlarged and his urine contained quantities of urobilin. After the patient had adhered to a strict diet, and completely abstained from alcoholic beverages, the liver condition improved, and thereupon the photosensitivity vanished. Barber, Howitt, and Knott¹⁶¹⁵ reported several cases in which treatment of a gastro-intestinal disease was followed by marked retrogression of skin manifestations. These authors are of the opinion that the light hypersensitiveness was attributable to a bacterial toxin formed in the intestine. D'Amato¹⁶¹⁶ observed a woman whose manifestations appeared only during her menstrual period. When menstruation was temporarily inhibited by roentgen irradiation, the patient's light hypersensitiveness disappeared, but it promptly recurred as soon as menstruation returned. Lancaster¹⁶¹⁷ found that in 5 cases the correction of menstrual disturbances by estrogenic substances was followed by a permanent restoration of tolerance to sunlight. Similar observations were re-

¹⁶⁰⁷ CAYEN, W. R. *J. Allergy* 3, 311, 1932.

¹⁶⁰⁸ STEIN, R. O. *Zentralbl. f. Haut- u. Geschlechtskr.* 25, 66, 1928.

¹⁶⁰⁹ RAJKA, E. *ibid.* 45, 521, 1940.

¹⁶¹⁰ CALLAWAY, J. L. *Arch. Dermat. & Syph.* 41: 889, 1930.

¹⁶¹¹ EPSTEIN, S. *J. Invest. Dermat.* 5, 187, 225, 285, 299, 1942.

¹⁶¹² URBACH, E., and BLOECH, J. *Wien. klin. Wchnschr.* 47: 527, 1934.

¹⁶¹³ BARBER, W. H., HOWITT, F. D., and KNOTT, F. A. *Guy's Hosp. Rep.* 76: 314, 1926.

¹⁶¹⁴ AMATO, G. D'. *Policlinico (sez. prat.)* 33: 150, 1926.

¹⁶¹⁵ LANCASTER, A. H. *South. M. J.* 32, 495, 1939.

ported by Thurmon¹⁶¹⁶ and Brunsting,¹⁶¹⁷ and were also made by the senior author Stokes and Calloway¹⁶¹⁸ have called attention to the development of sensitiveness to light in patients with either systemic or local infections. Sonck¹⁶¹⁹ reported a case of light hypersensitivity in a patient suffering from lympho granuloma inguinale, following a radical operation (extirpation of the rectum), the photosensitivity disappeared. Urbach and Shay¹⁶²⁰ recently published a case of extreme light hypersensitivity directed against the ultraviolet rays, which was completely and rapidly cured after cholecystectomy of a chronically inflamed gallbladder containing stones, the

a few days, and finally leads to pigmentation. Photo allergy, on the other hand, designates the condition observed in certain of these subjects who, on the tenth day after the test, spontaneously developed an inflammatory reaction with intense pruritus at the site of the primary reaction. These symptoms persisted from ten to fourteen days. Every subsequent exposure of these sensitized persons to ultraviolet light produced the same urticarial inflammatory response, now appearing not after ten days, but from ten to twenty-four hours after the test.

Pathogenetically, a distinction is made between *exogenous* and *endogenous* diseases of

TABLE 37—Photosensitizing Substances

Oral Route	Local Contact	Intravenous Route
IN MAN		
sulfonamides	sulfonamides	sulfonamides
eosin	eosin	gold
sulfonal	oil of bergamot	acridine, trypanflavine
barbiturates	oil of lavender	rose bengale
	oil of cedar	hematoporphyrin (Meyer Betz)
	vanillin oil	
IN ANIMALS	eau de Cologne	
buckwheat	coal tar	
clover	pitch	
Sudan grass	certain dyed fabrics	
St. Johns wort	certain plants (<i>Pastinaca sativa</i> , <i>Heracleum</i> , <i>Ruta</i> etc.) probably owing to furo	
<i>Lachnanthes</i>	cumarins	
<i>Tribulus</i>	phenothiazine (insecticide)	

patient also had an abnormal intestinal flora. Ayres, Jr.,¹⁶²¹ regarded the presence of entamoebas in the stool as a predisposing factor in a case of light hypersensitivity.

Epstein¹⁶²² draws a sharp distinction between primary photosensitivity due to photodynamic action and allergic photosensitivity (photo allergy). The former term indicates that in all individuals an intracutaneous injection of sulfanilamide, for example, followed by irradiation with ultraviolet light, results in a local erythematous reaction that begins to fade after

photosensitization, depending on whether the photosensitizing agent comes from without or is produced within the organism itself.

In cases of the *exogenous* type, the agent enters the body by mouth (either in foodstuffs or in drugs) or by parenteral injection, or exerts its allergizing influence by local contact (see Table 37). Light dermatoses caused by ingestion of photosensitizing substances are encountered almost exclusively in animals (cattle, pigs, sheep), and are usually found to be due to certain plants, such as buckwheat (*Fagopyrum*), St. Johns wort (*Hypericum*), wilted "dubbeltje" plant (*Tribulus*), clover (*Trifolium*), agave (*Agave lechuguilla*), and paintroot (*Lachnanthes*). Two principal disease pictures are observed: fagopyrism and "yellow thick head." In fagopyrism—so termed because the symptoms were first observed follow-

¹⁶¹⁶ THURMON F. M. presented before Section on Dermatology A. M. A. Atlantic City June 12, 1942.

¹⁶¹⁷ BRUNSTING L. A. discussion to Thurmon 1942.

¹⁶¹⁸ STOKES J. H. and CALLAWAY J. L. Arch. Dermat. & Syph. 36: 976, 1937.

¹⁶¹⁹ SONCK C. E. Acta dermat. venerol. 22: 499, 1941 (suppl. 6).

¹⁶²⁰ URBACH E. and SHAY H. Ann. Allergy 3: 124, 1945.

¹⁶²¹ AYRES S. JR. Arch. Dermat. & Syph. 29: 926, 1934.

ing ingestion of fagopyrum—only the unpigmented skin areas are involved. The skin manifestations consist of intense itching, erythema, and swelling; they can be as severe as those of an erysipelas, and are associated with a state of agitation. The symptoms are observed almost exclusively in the early spring when the animals are turned out of their winter stalls into the fields, where they are exposed to sunlight. Chick and Ellinger¹⁶² showed that rats could be experimentally sensitized to light (yellow-orange portion of the visible spectrum) by a diet of ground whole buckwheat seeds, but not if the husks were removed. The young flowers were most active in this respect. Other plants, particularly of the *Tribulus* species, provoke progressive icterus, which is followed by light hypersensitiveness generally localized in the unprotected areas of the skin. This results in a severe inflammation of the skin, which then presents a definite yellowish color, whence the name "yellow thick head."

With the exception of 1 case reported by Smith, fagopyrism in human beings is unknown. This is probably due to the fact that the active agent is altered in the cooking process, and thus becomes harmless. On the other hand, xanthoderma lipochromica seems to be at least partially due to the influence of light. At any rate, Klose described a yellowish discoloration following ingestion of carrots, observed only in those areas that were exposed to fairly strong sunlight—that is, chiefly on the face. This author also considers the effect of light to be the explanation of the fact that this coloration is observed almost exclusively in the summer and mostly in infants whose cribs are placed near a window.

Similarly, Hess and Myers¹⁶³ and Dollinger¹⁶⁴ assume that light plays a rôle in those cases in which, following ingestion of large amounts of spinach, a greenish color of the skin was observed only in those areas that had been exposed to sunlight (forehead, nose, cheeks, and hands).

Bommer's observation that an increase in light hypersensitiveness occurs when patients are put on a diet of raw foods, should perhaps be included here. He is of the opinion that

this may be explained by the fact that such a diet leads to an increased consumption of chlorophyll, which in turn may exert a photodynamic influence.

A similar mechanism may well be the basis of Riehl's melanosis. This is a dermatosis that Riehl, Sr.,¹⁶⁵ first observed during the first world war. The condition starts with circumscribed bluish-red erythematous patches, localized chiefly on the face, neck, chest, and back, followed by pigmentation of bronze to chocolate color. Etiologically Riehl linked the dermatosis with an alimentary intoxication (almost all of his cases had been eating bread made from beans). Kerl, on the other hand, assumed the presence of photodynamic substances in the ingested foods, and concluded that these substances sensitized the exposed skin areas to sunlight. This view has been quite generally accepted. Hoffmann attempted to find the photosensitizing substances not in foodstuffs, but in certain industrial products such as tar, naphtha, and coal. It was pointed out, however, that the picture of the melanosis was scarcely ever observed after normal nutritional conditions had been restored. Therefore, the designation "war melanosis of Riehl" seems apt.

Furthermore, light hypersensitiveness is not infrequently observed after oral administration or even topical application of sulfonamides (see pp 331, 393). Thus Park and Platts¹⁷⁵ reported the appearance of light dermatitis in 4.3 per cent of 486 soldiers in the Middle East receiving sulfanilamide, and 1.9 per cent of 309 receiving sulfapyridine. Photosensitivity occurred in 8 to 10 days of administration, and affected chiefly those parts exposed during chemotherapy or those previously exposed. Light hypersensitiveness occasionally ensues after dosage with barbiturates, sulfonal, eosin, and other drugs, when the patients are exposed to sunlight shortly after taking the medication. For this reason, they should be strongly advised to avoid direct sunlight for the duration of the treatment. Rimington,¹⁷⁶ Stryker,¹⁸⁷ and others attribute the sensitization to toxic damage that in turn results in the formation of porphyrin.

¹⁶² CRICK, N., and ELLINGER, F.: *J. Physiol.* 100: 212, 1941.

¹⁶³ HESS, A. F., and MYERS, V. C.: *J. A. M. A.* 73: 1743, 1919.

¹⁶⁴ DOLLINGER, A.: *Med. Klin.* 17: 1-33, 1921.

¹⁶⁵ RIEHL, G., Sr.: *Dermat. Wochschr.* 66: 318, 1918.

¹⁶⁶ ROBINSON, C.: *Lancet* 1: 770, 1938.

¹⁶⁷ STRYKER, G. V.: *J. Mississippi M. A.* 36: 484, 1939.

Among the substances that can produce light hypersensitiveness by local contact plants such as *Pastinaca sativa* *Heracleum Ruta graveolens* *Ficus* and *Dictamnus albus* represent the most important group. Kuske attributes this sensitizing action to the furanocoumarins contained in them. In addition certain essential oils such as bergamot oil (Freund, Gross and Robinson) and oil of orange flowers (Sams) are capable of exerting a similar effect. Starck¹⁶ demonstrated that parsnip root contains some substances capable of rendering the skin sensitive to a certain kind of radiation and that the sensitivity remains

fabrics (Epstein¹⁴⁵) and insecticides such as phenothiazine (De Eds, Wilson and Thomas¹⁴¹) can also act as photosensitizing agents.

Those diseases of sensitization in which a photodynamically active agent is formed within the organism are regarded as *endogenous*. The present state of our knowledge about these substances is rudimentary and in fact encompasses little more than those pigments that are called porphyrins.

To simplify matters somewhat we shall here consider the exogenously acquired and the endogenously formed porphyrin as belonging to one category nor incidentally is any sharp differentiation imperative since exogenous porphyrin can exert its photodynamic action only under certain very definite internal conditions.

There are two sources of *exogenous* porphyrin. First preformed porphyrin enters the organism in ingested animal protein (e.g. uncooked meat) but produce particularly grains and vegetables also contains porphyrin although in smaller amounts. Second spore bearing anaerobic bacteria in the intestines can form porphyrin both from the hemoglobin and myoglobin of ingested animal muscle and from the chlorophyll in vegetable foods.

Porphyrin can be produced *endogenously* in various ways from bleeding gastric and duodenal ulcers from disintegrating tissue protein from destroyed blood corpuscles and as the result of liver damage. Finally certain intestinal bacteria can produce porphyrin synthetically in the intestine from foodstuffs free of animal protein and chlorophyll. It is believed that they synthesize porphyrin from the pyrroles of the food.

It is a known fact that porphyrin occurs in the urine and/or stools of many light hypersensitive patients in quantities far greater than the mere traces found in the excreta of normal subjects. It is noteworthy that in certain cases of light dermatosis appreciable amounts of porphyrin can be found only in the stool (FIG. 201) and not in the urine and blood. This nearly always occurs in association with a pathologic intestinal flora or hepatic disturbances (Urbach¹⁶²). A diet free from ani-



FIG. 201 PORPHYRIN CRYSTALS IN STOOL OF PATIENT WITH STERCOPORPHYRIA AS SEEN WITH FLUORESCENCE MICROSCOPE

for some time after the exposure to the plant while the juice of the parsnip itself has no perceptible irritating influence on the skin. She reported 13 cases of local light sensitivity in workers handling parsnips. Klaber¹⁶²⁹ introduced the term phytophotodermatitis to apply to all types of photosensitization of the skin by plants and plant extracts. Gougerot and Hellier pointed to the eosin in lipsticks as the cause of cheilitis resulting from photosensitization. Coal tar and pitch (Foerster and Schwartz¹⁶³⁰) some crude oils certain dyed

¹⁶ STARCK V. A. *ta de mat. ven. col.* 25: 179, 1944.

¹⁴⁵ KLABER R. B. *t. J. De mat.* 54: 193, 1942.

¹⁴¹ FOERSTER H. R. and SCHWARTZ L. A. *h. Dermat. & Syph.* 39: 52, 1939.

¹⁴ EDS F. DE W. LEON R. H. and THOMAS J. O. *J. A. M. A.* 114: 209, 1940.

¹⁶² URBACH E. *Klin. Wchnsch.* 17: 304, 1938.

mal protein and restoration of a normal intestinal flora usually prevents the formation of enterogenous porphyrin and thereby results in the disappearance of the light hypersensitivity.

It must be admitted, however, that in any number of typical cases of light hyperseositivity, photosensitizing substances cannot be found in the blood, urine, or feces, this is especially true in xeroderma pigmentosum, which is characterized by an extreme degree of light hypersensitivity. This disease is probably the expression of a congenital abnormal reactivity to light within the range of the wave lengths from 2,970 to 3,100 angstroms (Lynch).

Pellagra must also be mentioned here. Spies,¹⁶³³ Ellinger,¹⁶³⁴ and their associates have found that this condition is characterized by a disturbance of the porphyrin metabolism, and that this, as well as all the other symptoms of pellagra, disappears after massive doses of nicotinic acid and adherence to a balanced diet. The increased porphyrin production in pellagra, together with the disturbances in the gastro-intestinal functions, is probably the result of avitaminosis.

However, the entire question of the relationship between porphyrins and light hypersensitivity is at present even more controversial than it was a few years ago. This is perhaps best illustrated by the fact that some authorities deny the etiologic importance of porphyrins, but hold that formation of them is a consequence of the destruction of skin tissue resulting from severe reactions to light. Since a detailed discussion of this problem is not possible here, the reader is referred to the excellent monographs by Blum,¹⁶³⁵ and by Dohrner and Rhoads.¹⁵³⁶

Finally, it is necessary—especially from the practical point of view—to discuss the type of light or the portion of the solar spectrum (visible light, long- or short-wave ultraviolet) that is responsible for sensitization to light. Thus, in a light dermatosis of the type of prurigo aestivalis, the senior author⁷²⁴ was able to prove that the hypersensitivity was

exclusively in relation to the yellow-red visible part of the spectrum of sunlight. The patient reported by Blum and West¹⁶³⁷ and Arnold¹⁶³⁸ was sensitive only to wave lengths in the spectral region between 3,900 and 5,300 angstroms—i.e., in the blue and violet parts of the visible spectrum. The case described by Erskin¹⁶³⁹ showed sensitivity only to the ultraviolet wave band. McKinnon's¹⁶⁴⁰ case, on the other hand, was found to be sensitive only to rays from the infra-red end of the spectrum. The same was true of Watkins' ¹⁶⁴¹ patient with urticaria from exposure to sunlight and infra-red heat lamps, the effective rays being confined principally to wave lengths from 7,900 to 14,000 angstroms. The portion of the spectrum responsible in a given case is determined by tests with appropriate light filters (p. 178). This differentiation is of practical importance in therapy, since the effectiveness of the various protective preparations depends on the wave lengths involved.

2. SYMPTOMATOLOGY

Light hypersensitivity is manifested in the majority of cases as an inflammation of the skin presenting a number of widely varying clinical pictures. Most frequently, there is an acute or subacute dermatitis (FIG. 202), often characterized by the presence of numerous bloody crusts. When the patient has been exposed to light for any considerable length of time, the skin condition may become chronic (FIGS. 203, 204), and even assume the appearance of a neurodermatitis (FIGS. 205, 206). In other cases the light diseases take the form of urticaria, prurigo, lupus-erythematosus-like dermatoses (FIG. 207), hydroa vacciniforme (FIG. 208) or aestivale (FIG. 209), and even of filiform, verruca-like lesions (FIG. 210) (Urbach and Wiethe,¹⁶⁴² Funck,¹⁶⁴³ Callaway,¹⁶⁴⁴ Wolfram¹⁶⁴⁵). In the same category are pellagrous skin inflammation (FIGS. 211, 212), xero-

¹⁶³⁷ BLUM, H. F., and WEST, R. J. J. Clin. Investigation 16: 261, 1937.

¹⁶³⁸ ARNOLD, H. L., Jr. Arch. Dermat. & Syph. 43: 607, 1941.

¹⁶³⁹ ERSKIN, D. Brit. J. Dermat. 54: 195, 1944.

¹⁶⁴⁰ MCKINNON, D. A. Proc. Staff Meet., Mayo Clin. 12: 333, 1937.

¹⁶⁴¹ WATKINS, A. L. Arch. Phys. Therap. 24: 291, 1943.

¹⁶⁴² URBACH, E., and WIETHE, C. Arch. f. Dermat. u. Syph. 148: 94, 1933.

¹⁶⁴³ FUNCK, C. F. Dermat. Wchnschr. 109: 1313, 1939.

¹⁶⁴⁴ CALLAWAY, J. L. Arch. Dermat. & Syph. 42: 350, 1940.

¹⁶⁴⁵ WOLFRAM, S. Arch. f. Dermat. u. Syph. 182: 434, 1941.

¹⁶³³ SPIES, T. D., GROSS, E. S., and SASAKI, Y. Proc. Soc. Exper. Biol. & Med. 38: 178, 1938; South. M. J. 31: 483, 1938.

¹⁶³⁴ ELLINGER, P., HASSAN, A., and TARA, M. M. Lancet 2: 1158, 1937.

¹⁶³⁵ BLUM, H. F. Photochemical Action and Diseases Caused by Light. New York: Reinhold, 1941.

¹⁶³⁶ DOHRNER, K., and RHOADS, C. P. Physiol. Rev. 20: 416, 1940.

derma pigmentosum and the melanos of Riehl. Furthermore light is potentially an eliciting factor in many cases of lupus erythematosus (FIG 213) and erythema exudativum multiforme. The significance of specific light hypersensitivity in these conditions is as yet *not entirely understood*.

While in all these cases the entire skin surface may participate in the reaction there are also certain localized contact photodermatides due

festations of the light dermatoses was recently controlled by Stokes and Beerman.¹⁶

Lehrfeld¹⁷ has suggested the existence of an ocular hypersensitivity to light related to urticaria solaris and accounting for certain types of visual intolerance of light or what the ophthalmologists term glare. It implies an inability to tolerate light of ordinary intensity and type and may result not only in conjunctivitis, ocular fatigue, photophobia, blepharospasm and headache but also reflexly in nervous irritability, general fatigue and easy physical exhaustion. Ocular pigmentary disturbances, trachoma and all acute inflammations of the anterior segment of the eye predispose to this condition. It may be treated by the wearing of tinted lenses.

3. DIAGNOSIS

The diagnosis of light dermatosis is arrived at on the one hand from the patient's report that the skin manifestations always appear following exposure to light and that they begin in the spring and disappear in the autumn and on the other hand on the basis of the fact that only the exposed skin areas are involved, i.e. primarily the face, neck (FIG 215), hands (FIG 216) and often the forearms and the uncovered part of the chest.

Simple diagnostic procedures are the mask method in which the patient wears a mask during the daytime or the dark room test, the patient remaining in a completely darkened room for three days (Dim artificial light is permissible). With the aid of these readily executed tests a case of acute (FIGS 217-218) or even chronic dermatosis (FIGS 219-220) can be diagnosed within three or four days to the extent of determining whether or not there is a hypersensitivity to light.

For a discussion of the methods of determining the causative rays in a given case by means of light filters the reader is referred to page 179.

Epstein¹⁸ has demonstrated at least three different types of reaction to tests with artificial light: (1) immediate urticarial or whealing reaction, (2) pathological sunburn like reaction and (3) provocation of the specific lesions of



FIG 207 ACUTE DERMATITIS DUE TO LIGHT HYPERSENSITIVENESS

to sensitization by locally applied ethereal oils such as oil of bergamot (FIG 183) and drugs or to the local action of plants.

In rare cases the light hypersensitivity may be of such extreme degree that diffuse urticarial responses can be evoked by exposure to ordinary daylight (FIG 214) even on a cloudy day. The writers observed a case of this kind in which the patient suffered general manifestations such as headache, lassitude, malaise and even fainting spells following a moderately long exposure to daylight.

An excellent review of the protean mani-

¹⁶ STOKES, J. H. and BEERMAN, H. *Am. J. M. S.* 203: 608, 1942.
204, 601, 1942.

¹⁷ LEHRFELD, L. A. *Arch. Ophth.* 23: 992, 1931.

prurigo. They correspond essentially to the clinical entities of *urticaria photogenica*, *dermatitis solare*, and *prurigo aestivalis*. While

local infection, an endocrine dysfunction, or a liver disease. Under these conditions, treatment according to the etiology is of course indi-

CHRONIC DERMATITIS OF HANDS DUE TO LIGHT HYPERSENSITIVENESS



FIG. 203 Before treatment

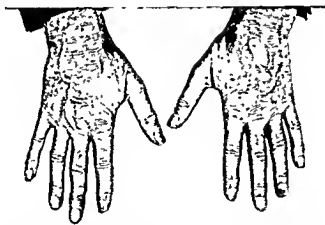


FIG. 204 After treatment with liver extract injections and living colon bacilli by mouth.

these three manifestations of hypersensitivity to light seem independent of each other, combined types occur.

4. THERAPY

The therapy of the conditions due to light is at present far from satisfactory. Attempts at hyposensitization with increasing doses of ultraviolet or other rays, as advocated by some authors, are as a rule of no avail.

In some cases it is possible to establish the fact that a certain drug or chemical is the photosensitizer; or that the disease is dependent on a gastrointestinal disturbance, a

cated. Pertinent cases have been mentioned above.

The liver disease itself may be caused by alcohol or syphilis, and in either case will require appropriate therapy. When the hepatopathy is pathogenetically obscure, it is advisable to prescribe a liver-sparing diet, high in carbohydrates and proteins, along with insulin injections. Injections of crude liver extracts should also be tried. Carrié⁶¹⁸ reported good results from feeding raw liver mash to rabbits that were eliminating increased amounts of porphyrin in the stool after toxic

⁶¹⁸ CARRIÉ, C. *Arch. f. Dermat. u. Syph.* 163, 523, 1931.



CHRONIC DERMATITIS DUE TO LIGHT HYPERSENSITIVENESS ON BASIS OF HEPATOPATHY, INTESTINAL DYSBACTERIA AND STERCOPORPHYRIA

FIG 205 Before therapy

FIG 206 After several weeks of treatment with living colon bacilli by mouth and injections of liver extract



FIG 207 LIGHT DERMATOSIS RESEMBLING LUPUS ERYTHEMATOSUS

doses of sulfonal the abnormal porphyrin elimination ceased and the hypersensitivity of the skin to ultraviolet irradiation disappeared

Good results are often achieved by the administration of 100 mg of niacin amide three times a day not only in pellagra but also in cases of light hypersensitivity of other origin (Gilman¹⁶⁹ Stokes⁶) O Leary¹⁵⁰ Capps and Young⁶⁵ and Epstein⁴ reported encouraging results following the use of his taminase three times a day from March until September. The senior author had good results in only 2 cases. In other patients of his as well as in many instances reported in the literature this treatment failed.

In a syndrome consisting of light dermatosis, hepatopathy, pathologic intestinal flora (dysbacteria) and fecal porphyria described by the senior author⁶² the porphyrin can be made to disappear by a strict animal protein free diet excluding meat, fish, poultry, eggs, milk and cheese for a period of four to five weeks. Amino acids may be used as substitutes for proteins in the diet. In addition to these measures *Bacillus acidophilus* preparations (along with lactose) or viable normal B

¹⁶⁹ C. E. HAN, R. L. d. usson to A. DERSON, N. P. A. h. De ma & Syph. 37: 822 (1935)

¹⁵⁰ O. LEARY, P. A. d. usson to L. A. MON, C. W. and CUMM. G. H. A. J. In est. De mal. 2: 301 (1939)

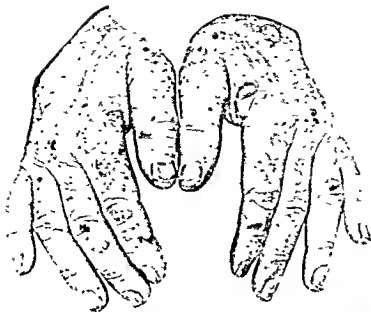


FIG 208 HYDROA VACCINIFORME BULLOUS AND ULCEROUS LESIONS

coli cultures (Mutaflor) should be given to correct the pathologic intestinal flora in which the normal colon bacillus has been replaced either by hemolytic *B. coli* or, as is more important, by *Streptococci* and *Staphylococci*. Buttermilk may also be tried. According to Schreus,¹⁶⁵¹ treatment should also include liver by mouth or injections of crude liver extract (3 cc. every second day). In cases of hepatic disease the present writers administer 10 units of regular insulin three times a day, shortly after the ingestion of adequate amounts of carbohydrates. With this regimen we have been able to obtain gratifying responses as shown by marked retrogression of the cutaneous symptoms along with the complete disappearance of fecal and urinary porphyrin, even in severe actinic dermatoses of many years' duration. The beneficial effects of a strict vegetable and fruit diet, reported by Anderson and Ayres,¹⁶⁵² may be attributed to similar basic principles. Russakoff and Blumberg¹⁶⁵³ reported that, in conjunction with dietary and vitamin therapy, choline chloride (3 Gm. twice



FIG 209 HYDROA AESTIVALE IN PATIENT WITH PORPHYRIURIA AND HEPATOPATHY (ALCOHOLIC CIRRHOSIS OF LIVER)

Note partial destruction of auricular cartilage

daily by mouth) is of benefit in cirrhosis of the liver.

In order to illustrate the beneficial influence of the therapeutic regimen described above on

¹⁶⁵¹ SCHREUS, H. T. Eighth Internat. Cong. Dermat. & Syph. Copenhagen, 1930.

¹⁶⁵² ANDERSON, N. P., and AYRES, S., JR. *J. A. M. A.* 103: 179, 1934.

¹⁶⁵³ RUSSAKOFF, A. H., and BLUMBERG, H. *Ann. Int. Med.* 21: 845, 1944.

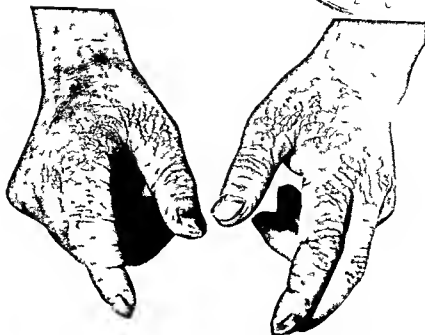


FIG. 210. LIPOID PROTEINOSIS (URBACH-WIETHE). RARE TYPE OF DISEASE OF LIPOID METABOLISM. Verruca-like lesions are due to concomitant effect of exposure to sun.

ALCOHOLIC ISMIDIOPELLAGRA ON BASIS OF PORTAL
CIRRHOSIS, INTESTINAL DYSBACTERIA AND
STERCOPORPHYRIA



FIG. 212. Atrophy and pigmentation of skin.

the clinical syndrome of light dermatosis, porphyria, hepatopathy and pathologic intestinal flora. Two cases are presented in detail.

Case 1. A 50-year-old man, whose father had also suffered from rather severe light hypersensitivity, gave a history of attack of bloody colic and migraine of many years duration following tonsillectomy.

When done because of an arthritis of the spine, there appeared on the exposed areas of the body a severe dermatitis which finally assumed an erythematous character. The light hypersensitivity became so distressing that he was forced to stay in a dark room for nine months. On admission to the hospital the patient presented an extremely severe exudative dermatitis of the face (Fig. 203), neck and hands (Fig. 203). Tests for photosensitivity showed an exudative dermatitic reaction four hours after exposure to ultraviolet



FIG. 211. Facial involvement confined to areas exposed to light.

light at a distance of 50 cm. for 20 seconds, and to direct sunlight for one minute



FIG 213 LUPUS ERYTHEMATOSUS DISSEMINATUS PROVOKED BY SUNLIGHT

Note that lesions are confined to exposed areas.

glycocoll (glycine) tolerance test revealed marked impairment of hepatic function, the figures being as follows: fasting 8 mg. per cent, peak after 25 Gm. of glycocoll 14 mg. per cent (an increase of 75 per cent), and after three hours when the original fasting level should have been reached, 12.2 mg. per cent. The patient was put on a strict sugar water diet for four days with the result that the fecal porphyrin disappeared. Simultaneously the clinical manifestations markedly improved, however it should be emphasized that at the time the patient was in a completely darkened room. A diet consisting solely of vegetables was then instituted for six days, at the end of which period the stool was still free from porphyrin. At this point the patient was given moderate amounts of boiled beet with the result that in 36 hours porphyrin reappeared in the stool, although in smaller amounts than



FIG 215 TYPICAL DISTRIBUTION OF LIGHT DERMATOSIS

Involvement is confined to areas exposed to light

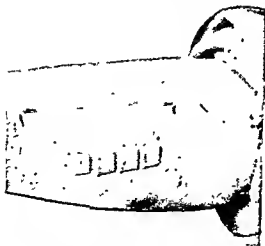


FIG 214 URTICARIAL RESPONSE TO LIGHT TEST THROUGH LIGHT FILTER

Positive reactions produced by sunlight and by its ultraviolet, blue green, and yellow portions, respectively.

While examination of the urine for porphyrin was negative, the stool was strongly positive by fluorescence microscopy and also by spectroscopy. The galactose tolerance test for liver function was normal, but the

formerly. Return to a vegetarian regimen again caused porphyrin to disappear after eight days.

Bacteriologic investigation of the stool showed that when the patient partook of a normal diet and the stool contained an abundance of porphyrin, the intestinal flora was characterized by a strain of *B. coli* with atypical cultural and staining properties, and, in addition, by the presence of large numbers of *Streptococci* and yeasts. By excluding food containing animal protein, a decrease in *Streptococci* and yeasts was achieved, but there was no change in the characteristics of the atypical *B. coli*. Therapy with viable culture of normal *B. coli* (*Mutaflo*) for eight weeks in order to correct the dysbacteria, along with the animal protein free diet resulted in the establishment of a normal strain of *B. coli*. In addition the patient was given 3 cc. of crude liver extract by intramuscular injection every second day. This combined therapy accomplished (1) a marked decrease of the light sensitivity so that the patient

could tolerate daylight but not direct sunlight without experiencing skin manifestations (T_gs 204-206 °C) and disappearance of fecal porphyrin on a normal diet (3

per cent an increase of only 39 per cent) and after three hours 87 mg per cent. Despite the dietary restriction the patient had gained 12 pounds

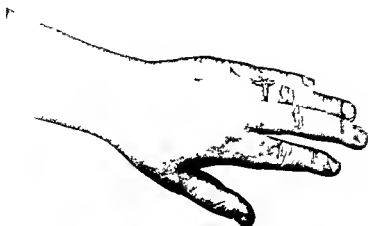


FIG. 216 SIMPLE CLINICAL TEST FOR LIGHT HYPERSENSITIVENESS

Exposure of hand to bright noon sunlight for ten minutes produced acute erythema and edema



FIG. 217 Acute dermatitis of face and neck, emptying parts ordinarily covered by hair



PROOF OF LIGHT HYPERSENSITIVENESS BY SIMPLE CLINICAL METHODS

FIG. 218 Same patient after forty-eight hours in darkened room. Similar effect can be obtained by wearing black mask

improvement in the liver function as shown by the glycocholic acid tolerance test the figures now being fasting 7.2 mg per cent peak after 25 Gm of glycocholic acid 10 mg

Case 2 A 52-year-old woman had had infantile dermatitis in childhood since which time she almost continuously had a light dermatitis on the basis of a

rather marked ichthyosis. During her first pregnancy at the age of 22 years the patient had jaundice for about one month, but this did not appear during two subsequent pregnancies. Following exposure to sun light during a cruise, a severe dermatitis developed on the unclothed parts of the body. A diseased gall-bladder which was thought to be the cause was removed. Some months later the severe dermatitis recurred on the face, neck, and extremities after exposure to sunlight at the seashore for a short time. In addition to the jaundice mentioned above the fact that the patient for many years indulged freely in "social drinking" raised a suspicion of hepatic disease.

On admission to the hospital the patient exhibited a severe, partially oozing dermatitis of the exposed areas. The rest of the skin was markedly ichthyotic

tablespoon of lactose three times a day. In addition the patient was kept in a totally darkened room and received 10 units of regular insulin three times daily.

The dermatitic skin manifestations subsided entirely in about five days. However it was only after one month of the regimen described above that the liver function was normal as evidenced by the absence of bromsulfalein retention. The hemolytic *B. coli* and the *Streptococci* could not be recovered from the stool. However when protein hydrolysates or milk or cheese were added to the diet small amounts of porphyrin reappeared in the urine and the stool. At the same time moderate numbers of *Streptococci* were found in the stool culture. Porphyrin and the *Streptococci* were further slightly increased when meat was allowed. Nevertheless the patient could now tolerate exposure



PROOF OF LIGHT HYPERSENSITIVENESS BY SIMPLE CLINICAL METHODS

FIG 219 Chronic dermatitis. Porphyrin found in stool, probably owing to pathologic intestinal flora and hepatopathy.

FIG 220 Marked improvement after six days in dark room.

After three days on a meat-free diet, a hydrochloric acid extract of the urine gave strong fluorescence under ultra-violet light and showed spectroscopic bands characteristic of porphyrin. An ether extract of feces exhibited marked fluorescence and porphyrin bands while the hydrochloric acid extract presented moderate fluorescence and faint bands. Bacteriology of the stool revealed, in addition to normal *B. coli*, the presence of hemolytic *B. coli*, *Streptococcus undans* and *Streptococcus hemolyticus*. The bromsulfalein excretion test indicated impairment of hepatic function in that there was 25 per cent retention of the dye. The treatment consisted of a diet free of animal protein and animal and vegetable fat, but high in vegetables, fruits, and carbohydrates, injections of 3 cc of crude liver extract every second day, nicotinamide 100 mg three times a day, riboflavin 5 mg daily, yeast concentrate 2 tablets three times a day, and *Bacillus acidophilus* whey culture one tablespoonful with one

to normal daylight with impunity. The pathologic flora and the fecal porphyrin could be controlled by oral administration of penicillin (20 000 units eight times a day for about two weeks), but only so long as the patient took penicillin.

Jauston and Pagès suggest an entirely different approach—auto-urotherapy. The success of this method indicates that light hypersensitiveness may be due to the formation of an endogenous allergen. It is even conceivable that the porphyrins may assume the character of haptens and that the conjugated allergen is excreted in the urine.

Urbach and Kral¹⁵⁴ reported on protection

¹⁵⁴ URBACH, E., and KRAL, F. *Klin. Wochenschr.* 16: 960, 1937.

against light by means of a combination of vitamin C and oil of bergamot. These observations were confirmed by Nakajo,¹⁶⁵⁵ who added that he achieved a similar protective effect with vitamin B₂ as well as with adrenal cortical extract in combination with oil of bergamot. Miescher,¹⁶⁵⁶ on the other hand, was unable to corroborate these findings.

Of course if the patient will take the trouble to protect all exposed skin areas with appropriate lightproof ointments during the daytime, he will remain free of symptoms. According to the thorough spectrographic studies of Fantus and his associates,^{1657, 1658} the following prescriptions are particularly efficacious in cases of hypersensitiveness to the ultraviolet portion of the spectrum.

	Gm. or Cc
CUTICOLOR POWDER	
Red ferrous oxide	6 0
Yellow ferrous oxide	8 0
Titanium dioxide	86 0
LOTION	
Cuticolar titanium dioxide	15 0
Bentonite	2 5
Glycerin	15 0
Stronger rose water to make	100 0
CREAM SALVE	
Cuticolar titanium dioxide	30 0
Glycerin	1 5
Vanishing cream	70 0

Another helpful preparation is Max Factor's pancake make up.

Schwartz¹⁶⁵⁹ points out that these physical light screens block the passage of all light rays, but that chemical light screens can be used to prevent the passage of the burning rays (2,900 to 3,200 angstroms) but permit the passage of tanning rays (3,300 to 4,000 angstroms). A number of new and effective synthetic chemicals are available for this purpose, and appropriate formulas retain their screening properties for as long as four hours.

	Gm. or Cc
SUNTAN OIL	
Menthyl salicylate	10
Sesame oil	45
White mineral oil	44
Hydroquinone	0 2
Perfume	1

¹⁶⁵⁵ NAKAJO A. *Jap J Dermat* 44: 48 1938

¹⁶⁵⁶ MIESCHER S. *Schweiz med Wchnschr* 68: 888 1938

¹⁶⁵⁷ BACHMANN A. and FANTUS B. *Arch Phys Therapy* 20: 69 1939

¹⁶⁵⁸ FANTUS B. and DYNIEWICZ J. M. *J Am Pharm A* 27:

878 1938

¹⁶⁵⁹ SCHWARTZ L. *Am J Nursing* 44: 640 1944

SUNTAN CREAM	
Menthyl anthranilate	5
Sesame oil	15
Cholesterol	2
Cold cream	39
Vanishing cream	39

SUNTAN LOTION	
Butyl benzal acetone oxalate	2
Sesame oil	10
Tannic acid	1
Alcohol ethyl	86
Perfume	1
Hydroquinone	0 2

When the hypersensitiveness is in reaction to the yellow or red portion of the solar spectrum, the addition of resorcin (about 2 per cent) is necessary. If resorcinol or quinine derivatives are employed, it is advisable to perform patch tests first, since these drugs are potent sensitizers.

However, it can readily be seen that the burden of applying and wearing these salves or lotions, not only on the face but also on the ears, neck, forearms and hands, day after day, soon becomes intolerable.

E RAYS OTHER THAN LIGHT

In connection with hypersensitiveness to the visible portions of the spectrum the invisible rays of the electromagnetic series must also be considered.

Although some supportive evidence is at hand, it cannot as yet be definitely stated that roentgen grenz, and radium rays in themselves, can have allergenic action. Most authorities who have investigated the question are of the opinion that there is no such thing as hypersensitiveness to these rays. Certain observations, however—especially of the very rare instances of so called roentgen exanthema—indicate the necessity for further study in this direction.

A case reported by Schreiner¹⁶⁶⁰ will serve as a good example. "Thymus stimulating irradiation" was administered to a patient with lichen ruber planus. Proper care was taken to protect the surrounding areas. On the following day a sharply demarcated erythema was observed and after nine days almost the entire surface of the body was red and inflamed and in many areas covered with vesicles. Several days later, after all these skin mani-

¹⁶⁶⁰ SCHREINER K. *Strahlentherapie* 16: 389 1924

festations had vanished, a small area on the patient's back was irradiated with 100 r. Eight days thereafter the same skin manifestations reappeared.

Paltrinieri is of the opinion that certain skin and mucous membrane reactions appearing after irradiation are to be interpreted as allergic responses. He cites 8 cases. All had previously received massive doses of relatively soft roentgen irradiation, after very small doses of radium irradiation at a later date, the treated skin areas of all these patients presented marked erythema, swelling, and vesiculation, accompanied by fever. In this connection, Richet¹⁶⁰¹ cites the case reported by Bergonié. A physician was obliged to stop his professional activities (in so far as irradiation therapy was concerned) because of a roentgen dermatitis; when he resumed his work after a while, there was observed an extraordinary shortening of the time between the application of the rays and the appearance of the skin reaction—the latent period.

Richet is of the opinion that roentgen rays provoke a chemical alteration in the tissue cells, thereby producing substances that possess allergizing properties (auto-endogenous allergens, in our nomenclature). Schall goes so far as to speak of actinoproteins to which antibodies are formed, the period of latency corresponds to the time it takes for the antibodies to develop. The undulating phases characteristic of the roentgen reaction suggest, as Miescher pointed out, that, as in serum exanthems, the assumed formation of various actinoproteins leads in turn to the production of the corresponding antibodies, a process taking place at different times. Miescher holds that immunobiologic processes may well be at the basis of the roentgen reaction; but he grants of course that no definite proof to that effect is as yet available, since no demonstration has been made of the existence either of actinoproteins that might act as allergens, or of the antibodies with which they might enter into reaction.

Furthermore, a number of reports indicate that one type of irradiation can lead to sensitization or desensitization of the tissues to other rays and to physical agents generally. The whole problem, however, has not as yet been

adequately studied. But the frequent observation of one apparent paradox is noteworthy: the provocative, irritating effect of small and even minute doses of irradiation, and the inhibiting effects of larger and even massive doses (Kusnitzky and Guhrauer). For a complete bibliography, the reader is referred to Shaffer.¹⁶⁰²

According to Holthusen, the question of roentgen allergy is as confused as it is because of failure to take into consideration the cumulative effects of the rays, and because this is so very difficult to evaluate.

L. Freund calls attention to the increased sensitivity of the vascular system of the skin to all types of rays during the premenstrual period.

Finally, Mark's¹⁶⁰³ report is of great significance: He found that sulfanilamide sensitizes the skin to X rays, and that the sensitization persists even after the drug has been discontinued for some time.

F. PRESSURE

Dermographism, or urticaria factitia—urticaria due to stroking—is generally not to be regarded as a physical allergy, but rather as an expression of vasomotor neuropathy, sometimes probably due to traumatic liberation in the skin of histamine-like substances that induce a localized wheal response (Lewis). However, there are some cases of this kind in which the sensitivity is of such high degree that Doerr's four criteria for designating a condition as allergic—including the passive transfer test—are easily fulfilled; and such cases must, therefore, be recognized as examples of physical allergy (A. Walzer,¹⁶⁰⁴ Lehner,¹⁶⁰⁵ Prieto,¹⁶⁰⁶ Tosatti¹⁶⁰⁶).

Urticaria factitia is not to be confused with pressure urticaria. The former is provoked within a few minutes by a gentle superficial mechanical influence, such as stroking of the skin, the latter, on the other hand, appears only after a latent period varying from two to twenty-four hours and only at the site of relatively great pressure. While in some cases pressure urticaria may appear in fifteen or

¹⁶⁰² SHAFER, B. J. *Invest. Dermat.* 3: 159, 1940.

¹⁶⁰³ MARKS, M. B.: *J. Pediat.* 16: 503, 1940.

¹⁶⁰⁴ WALZER, A. *Arch. Dermat. & Syph.* 18: 558, 1929.

¹⁶⁰⁵ PRIETO, J. G. *Actas dermo-sif.* 24: 404, 1932.

¹⁶⁰⁶ TOSATTI, P. M. *Policlinico (sez. med.)* 43: 205, 1936.

¹⁶⁰¹ RICHTER, C.: *Compt. rend. Acad. d. sc.* 162: 614, 1916.

twenty minutes, it most often sets in much later and the relationship to pressure several hours before is frequently overlooked. Pressure urticaria is a most distressing affliction, manifested as urticarial or edematous swellings of the feet, for example on walking on the hands when the individual is at work, and on the buttocks when seated.

The writers' observations show that such manifestations of pressure urticaria are not by any means always of allergic origin, in fact the condition can very frequently be attributed to a nonallergic pathergy—or in other words, to a vascular hypersensitiveness resulting from infection, intoxication, and similar conditions.

A case in question was that of a soldier whose urticarial manifestations appeared after fish poisoning and were particularly severe when the skin was subjected to prolonged pressure—for example on the hands when the patient was drilling with his rifle. Experimental application of pressure evoked late urticaria appearing after four hours. Attempts at passive transfer with blood serum and blister fluid were unsuccessful. Study of the patient disclosed a jejuno-ileitis. A cellulose poor, milk rich diet was prescribed, and the pressure urticaria soon showed marked improvement, return to coarse bulky food brought on a severe recurrence of the condition. After strict adherence to the special diet for several months, the patient was finally entirely cured. This case may be regarded, therefore, as one of specific but non allergic hypersensitiveness to pressure—in other words, as an example of nonallergic pathergy. A comparable instance was observed by Stokes¹⁸⁸⁸ an urticaria due to the pressure of a truss but appearing only when the patient was suffering from an acute enteritis.

In another case of the senior author¹⁸⁶⁸—one of especially severe late urticaria due to pressure—the passive transfer test also failed. The patient presented an immense urticarial wheal that began to develop several hours after the exposure to pressure and attained its maximum size about twenty four hours later, persisting for another two days. It must not be overlooked, however, that such cases may very well be instances of endogenous allergy, this would make it impossible, of course, to

obtain the allergen for experimental antigen-antibody reactions.

Both Andrews¹⁶⁶⁷ and Gottron¹⁶⁶⁸ found evidence of porphyrimuria in their cases. These authors assume that pressure urticaria is attributable to liver disturbances.

G MECHANICAL STIMULI

It was Duke⁵⁰⁰ who first suggested that a state of allergic hypersensitiveness might be brought on by mechanical influences. He assumed that in such cases the patient acquires a specific hypersensitiveness to substances produced in his own tissues under the effect of mechanical stimuli. These substances are tissue proteins so altered by the physical influences that they become foreign to the body and thereby act, according to our definition, as auto endogenous allergens.

Experimental proof of the fact that allergization can be caused by a mechanical insult was first advanced by Urbach and Steiner.⁶⁹¹ Their patient, an inspector in a barley cleaning establishment, had had a widespread dermatitis ever since he had begun to work in this plant. The condition cleared up rapidly when the patient stayed away from the place for a few days. Patch tests revealed barley dust as the allergenic agent (Fig. 221), it was also discovered that the patient reacted only to the residue remaining after extraction of the barley dust but not to aqueous or alcoholic extracts. The actual cause of the condition was found to be the silicated plant hairs (so called trichomes) from the barleycorn shells these sharp particles which were found in large quantities in the barley dust (Fig. 222), bored their way into the follicles of the skin and there caused an allergic inflammation, histologically characterized by vesicles and numerous eosinophile cells in the epidermis (Fig. 223). The assumption that mechanical insults were to be regarded as an allergenic factor in this case was supported by the production of similar irritation by pulverized glass wool, and still more by the successful transfer of the hypersensitiveness by means of fluid from a can

1667 ANDREWS G. C. *discuss on to* LEWIS G. M. Arch. Dermat. & Syph. 39: 365, 1939.

1668 GOTTRON H. and LEVOT V. Arch. f. Dermat. u. Syph. 179: 308, 1939.

tharides blister induced on the specifically irritated skin. The degree of the hypersensitivity was revealed by the fact that strong reactions were elicited by patch tests with 0.01

within a few days had an itching skin eruption over his entire body. Since relief from this condition was afforded only by avoidance of the establishment, he was obliged to seek another occupation and was completely free from skin disease for thirty years—until he was again employed in a barley-cleansing plant.

A second case was that of an elderly agriculturist who for two years had suffered such intense attacks of itching in the threshing season that he was forced to give up this work. Application of barley dust in a patch test elicited intense itching and a severe follicular inflammation that became vesicular.

A third case was that of a servant on a farm who regularly acquired a distressing skin eruption on exposed areas, along with acute rhinitis, conjunctivitis, and laryngitis, whenever she engaged in threshing barley—and at no other time. Patch tests with barley dust were positive.

Comparable cases were reported several years later by Duke,¹⁸⁷⁰ who described them as "wheat muller's asthma." He reported that these workers reacted intensely to dust obtained from the first cleansing of the wheat



FIG. 221. POSITIVE PATCH TEST WITH BARLEY DUST



FIG. 222. POINTED SILICIFIED PLANT HAIRS (TRICHOMES) IN BARLEY DUST, REPRESENTING PHYSICAL ALLERGEN

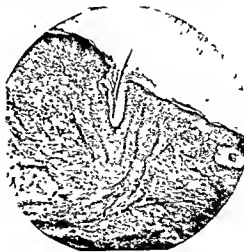


FIG. 223. SILICIFIED PLANT HAIR (TRICHOME) IN FOLLICLE OF SKIN, GIVING RISE TO EOSINOPHILIC REACTION

per cent of barley dust in petrolatum and with 1 per cent barley dust in zinc oxide. The patient's history is noteworthy: at the age of 14 he began work in barley-cleansing plant, and

and that this dust contained many sharp-pointed hairs originating from the grain spike. He successfully performed passive transfer of the hypersensitivity to normal skin.

In addition there are a few similar clinical observations in which the allergic nature of the cases unfortunately was not proved by passive transfer. These reports include Pastor cutaneous nasal and conjunctival hypersensitiveness to finely pulverized straw particles resulting from threshing; Michelson asthma with attacks occurring only at the scene of threshing; Szentkiralyi dermatitis due to so called angel's hair—i. e. finely spun glass wool used for decorating Christmas trees; and

Alderson and Rawlins inflammation of the skin in rice polishers.

Needless to say those mechanical injuries to the skin that are caused by stingers of insects or nettles of plants that break off on contact with the skin and introduce the noxious substance very much in the manner of a hypodermic injection are to be excluded from consideration as physical allergies. They belong to the category of toxic or allergic injectants.

CHAPTER XVIII

INFECTANTS

ALTHOUGH the subject has been most extensively investigated, the rôle of bacteria, viruses, and fungi as allergenic agents is as yet very little understood. In considering this question, it must always be borne in mind that with bacteria and probably also with other infectious agents, an allergic response can be elicited by two entirely different mechanisms—one mediated by the toxins, and the other by the bacterial proteins or carbohydrates.

When *toxins* are absorbed in the course of infection, they create an immunity, immunologically expressed by the formation of antibodies called antitoxins, provided the human or animal organism wins the struggle against the invading bacteria. Individuals who have overcome the disease, and whose blood therefore contains an adequate antibody titer, fail to react to skin tests with toxin, and thus give evidence of their state of immunity. Positive reactions to such skin tests, on the other hand, suggest susceptibility to the given toxin-producing bacteria. It is on this principle that the Schick test for diphtheria, the Dick test for scarlet fever, and the erysipelas toxin test are based.

The reaction of the organism to living or dead *bacteria* (or viruses) is, however, quite different. These agents evoke the formation of antibacterial antibodies, chiefly in the tissues. In patients suffering from or recovered from an infection, bacterial antigen used for skin testing reacts with these cellular antibodies, as manifested most commonly by delayed-inflammatory and only occasionally by immediate wheal responses. On the other hand, healthy individuals and persons who have never had the particular infectious disease, fail to react. This reactivity of the infected organism to bacterial or viral antigen is the basis of the skin tests for the diagnosis of infectious diseases. An outline of the clinically useful skin tests will be found in Table 38.

Microbial allergy plays a part in the onset of infection, in the clinical manifestations of the disease, in the course of the infection (as re-

gards its remaining localized or becoming generalized), and lastly in its outcome.

For a discussion of the significance of bacterial diseases as a factor predisposing to allergy, see page 63.

A. BACTERIAL HYPERSENSITIVENESS

Can bacteria, viruses, and fungi, in themselves, produce states of hypersensitiveness? This question must be unequivocally answered in the affirmative, and both bacterial anaphylaxis and bacterial allergy must be included in this statement.

Rosenau and Anderson (1907) showed that reinjection will produce anaphylaxis in guinea pigs sensitized with dead typhoid or tubercle bacilli, as well as with yeast. On the other hand, the vaccines used for testing and treatment are by no means identical with the bacteria that infect and thereby sensitize the organism, for the vaccines come from bacteria grown on artificial media and altered by heat or chemicals. That this anaphylaxis was of the true experimental type, just as in serum anaphylaxis, is demonstrated by (1) classic shock in the sensitized animal; (2) passive transfer, and (3) positive reactions with the Dale uterine strip method. However, because of the low antigenicity of bacteria, relatively large amounts of the vaccines were necessary both for sensitization and for elicitation of the shock. Zinsser and his associates, Tomcsik and Kurowschkin, and Baldwin and Rich, as well as others, have shown, furthermore, that under certain conditions experimental anaphylaxis can also be readily achieved by employing products derived from bacteria. The antigenic property seems to be contained not only in protein extracts, but particularly in the specific polysaccharides of the bacteria (Heidelberger and Avery). However, the literature does not, to our knowledge, contain mention of any instance of bacterial anaphylaxis in human beings.

1. BACTERIAL ALLERGY

With the exception of the fulminating hemato-genous processes and those accompanied by

cachexia (see p 24), every infection in man and in animals leads first to a state of hypersensitiveness to the micro organism, this, in certain infectious diseases, is in turn replaced by a state of temporary or permanent immunity (The interdependence of allergy and immunity is discussed more fully on p 18)

trichophytin type reaction, and (2) rather rarely, the immediate-urticarial or wheal type. The latter is seen relatively more commonly in reaction to molds and *Monilia* than to bacteria or trichophytin. In addition (3) an eczematous or epidermal-contact type of reaction is known to occur, although infrequently,

TABLE 38—*Skin Tests Employing Antigens of Bacterial and Viral Origin (Kane¹⁹⁴⁴)*

Test	Material Employed	Time Read	Size of Positive Reactions	Interpretation of Positive Reactions
EMPLOYING BACTERIA AND THEIR PRODUCTS AS ANTIGENS				
Tuberculin	P P D or O T	48 hr	Edema and erythema greater than 5 mm	Previous infection
Brucellergin	Brucellergin	48 hr	Edema and erythema greater than 5 mm	Previous infection
Chancroid	Vaccine (heat killed bacilli)	48 hr	Edema greater than 8 mm and erythema greater than 14 mm	Previous infection
Pertussis	Detoxified agglutinin	15 min and 24 hr	Wheal in 30 min or induration and erythema greater than 10 mm in 24 hr	Questionable immunity
Tularemia	Detoxified antigen	48 hr	Edema and erythema greater than 10 mm	Previous infection
Francis	Specific pneumococcus carbohydrate	15 min	Wheal and erythema	Excess circulating antibody
Influenza bacillus infection	Specific influenza bacillus carbohydrate	15 min.	Wheal and erythema	Excess circulating antibody
EMPLOYING BACTERIAL TOXINS				
Schick	Diphtheria toxin	48 and 96 hr*	Edema and erythema greater than 10 mm*	Susceptibility
Dick	Erythrogenic streptococcus toxin	24 hr	Erythema greater than 10 mm	Susceptibility to erythrogenic toxin
EMPLOYING ANTIGENS OF VIRAL ORIGIN				
Frei	Inactivated lympho granuloma venereum virus	48 hr	Induration at least 5 or 6 mm	Previous infection
Enders	Inactivated mumps virus	24 and 48 hr	Erythema greater than 10 mm	Immunity

* There is a great deal of variation in the literature as to what should be considered a minimal positive reaction and also as to when the test should be read

Depending on the manner of administration of the antigen (cutaneous, intravenous) and on the quantity administered, the hypersensitiveness manifests itself in a local, focal, and/or systemic reaction. Two principal types of skin reactions to microbial allergens are observed (1) more commonly, the delayed-inflammatory or tuberculin type or

it may be elicited at times with trichophytin or oidiomycin in some cases of dermatitis. As a matter of fact, in infectious or microbial dermatitis, all three forms of sensitivity can be observed.

The relation and significance of the two principal forms of reactivity has been considered in some detail in the section on skin

reactions (p. 163). The majority of the students of this question are of the opinion that the same basic mechanism is involved in these two expressions of hypersensitiveness. According to Bronfenbrenner,¹⁶⁵ the delayed reaction in response to intradermal injection of bacteria is due largely to the complexity of their composition, their physical state, and to the relatively low immunogenic properties of bacterial antigens. Wells,¹⁶⁶ Zinsser,¹¹ Vaughan,⁷¹ and others explain the rarity of the immediate reaction by the fact that, in the course of the preparation of the bacterial extracts, the proteins are denatured by heat or chemicals. Heat-killed tubercle bacilli, injected into tuberculous guinea pigs, produce the tuberculin type of skin allergy, while ground tubercle bacilli elicit in guinea pigs an immediate wheal with erythema (Wells¹⁶⁶). Bacteria (e.g., pneumococcus) from which the antigen may be obtained by the simple process of autolysis, quite frequently produce immediate-urticarial reactions (Zinsser et al.¹¹). In cases responding with an early wheal reaction to bacterial extracts, Forman¹⁶⁷ and Caulfield¹⁶⁷ were able to achieve passive transfer of the hypersensitiveness. On the other hand, soluble proteins, such as egg white, can evoke a delayed-inflammatory (tuberculin-type) response, provided the first administration of the antigen is made in a site in which an inflammatory process has been induced (Dienes and Schoenheit¹⁶⁷).

Lastly, mention must be made of those immediate specific reactions that are not urticarial but erythematous-edematous in character, and that follow injections of antiserum into the skins of individuals infected by the micro-organism with which the antiserum was prepared (Foshay¹³¹). Tamura¹⁶⁷ made use of this principle in the case of patients with lymphopathia venerea: he claims that the reaction to an anti-Frei-antigen goat serum is specific, and may be used as a means of quick diagnosis.

In practice—at least with the commonly used bacterial vaccines and extracts—the reactions encountered are almost exclusively of

the delayed type. The first question that arises is as to whether a positive skin test represents merely an aftermath of a former infection, or whether it is an indication of an existing illness. This question must be separately considered in each case, and it is not always easy to arrive at the correct answer, especially when dealing with streptococci and staphylococci. Furthermore, opinions are sharply divided as to whether or not a positive reaction is to be considered specific. On this question, the writers side with Famulener,¹⁶⁷ Thomas and Touart,¹⁶⁴ Brown,¹⁶⁷ and the many others who hold that delayed reactions to bacteria, at least, are potentially specific, and for the following reasons: the positive reaction is consistently obtainable until modified by repeated desensitizing injections, the positive late reaction is often accompanied by focal or systemic manifestations, old quiescent test or treatment sites have quite often been lighted up by subsequent injections of the same vaccine; and, by and large, the intensity of the reaction decreases as the symptoms recede.

The concept that the delayed reaction is truly allergic has been attacked on the grounds that (1) a reaction of this kind does not occur in nonbacterial protein allergy, (2) antibodies are not demonstrable in the serums of the patients, i.e., passive transfer tests are negative, (3) good therapeutic results are no proof of specificity. In reply to these objections it may be said that, under certain conditions, delayed reactions can be brought about by nonbacterial proteino-genous allergens (see p. 163), that failure of passive transfer with blood serum indicates merely the absence of serum antibodies, since in some of the cases cellular antibodies can be demonstrated by other methods (e.g., Dale's uterine strip technic). Moreover, a number of positive passive transfers have been reported: thus, Sprouck, Zinsser, and Konrad have successfully transferred tuberculin hypersensitiveness, and Sulzberger and Kerr have transferred trichophyton hypersensitiveness.

Rich⁷¹ is inclined to believe that bacterial hypersensitiveness depends upon a specific

¹⁶⁵ BRONFENBRENNER, J. J. *Lab. & Clin. Med.* 26: 102, 1940.

¹⁶⁶ FORMAN, J. *Ohio State M. J.* 31: 200, 1935.

¹⁶⁷ CAULFIELD, A. H. W., J. *Allergy* 2: 372, 1931.

¹⁶⁸ TAMURA, J. T. *J. Lab. & Clin. Med.* 21: 543, 1936.

¹⁶⁹ FAMULENER, L. W. *J. Allergy* 1: 84, 1929.

¹⁷⁰ THOMAS, W. S., and TOUART, M. D. *ibid.* 4: 242, 1933.

¹⁷¹ BROWN, G. T. *South M. J.* 27: 856, 1934.

antibody, for the following reasons (1) the high degree of specificity of the phenomenon (2) the anamnestic reaction, (3) the phenomenon of specific desensitization. He ventures the hypothesis that the antibodies are closely bound to the cells, and that there is an insufficient accumulation of excess antibody to permit passive transfer.

At this point the writers would like to give their own opinion on the subject—namely, that a specific allergic mechanism is the basis of the delayed inflammatory reactions, and that these reactions are characteristic of infectious allergies. The presence of infected tissue in the animal is an essential prerequisite for the production of this type of hypersensitiveness. The delayed inflammatory reaction is probably brought about by the liberation of the antigen—from the tubercle bacillus, for example, through the action of the cellular enzymes of the tubercle. Bacterial allergy is a hypersensitiveness to the somatic protein antigens of bacteria in which the cells become sensitized by the liberation of an unchanged protein bacterial substance in the lesions¹⁷ (Zinsser). On the other hand, the usefulness of allergic reactions as a diagnostic aid is curtailed in many infectious diseases by the fact that the allergic state persists long after the disease has subsided.

Next, it might be well to consider the question of the occurrence of bacterial allergy in healthy individuals. It is known that it is by no means a rare thing to encounter positive reactions to filtrates of pathogenic microorganisms in persons who are not only in perfect health, but who have never, as far as they know, been afflicted with the infectious disease. There are two schools of thought on the subject—one believing that bacterial allergy in a healthy individual signifies an increased susceptibility to infection, the other regarding it as indicating an increased resistance (immunity) to infection. The results of recent investigations make it appear likely that contact with infected material may result in the development of a state of hypersensitiveness unaccompanied by any clinical manifestations of the disease (a "silent," symptomless, "nonapparent," or subclinical infection, also called *formes frustes* or *stille Feyung* in the European literature). Thus,

Morales Otero and Gonzalez¹⁸ report that among milkers and cattle handlers in a certain region where endemic abortion in cattle is prevalent cutaneous hypersensitiveness to brucella antigen was shown by 30 per cent of the individuals tested whereas only 3 per cent had histories of undulant fever. Furthermore, 3 of 7 workers in the laboratory of these authors showed positive cutaneous reactions without signs or symptoms of the disease. Numerous similar examples could be cited. However according to the experimental work of Zinsser and Tamiya,¹⁷⁷ some of these allergic skin reactions may possibly be due to sensitization with other bacteria. Confirming this are the observations of clinicians (Arzt and Fuhs¹⁷⁸) that tuberculous patients and individuals giving strongly positive reactions to tuberculin very commonly react to tests with trichophyton and other extracts. These responses, according to our concepts, are to be interpreted as metallergic reactions (p. 28).

In addition to overt infections bacterial hypersensitiveness may arise from the absorption of bacterial substances and/or products from foci of infection in any one of a number of sites in the body (see Table 11). As discussed elsewhere, identification of such foci and proof of their etiologic significance is often difficult. An infectious source which is commonly unrecognized may be resident in the intestinal tract. Although the concept of toxic absorption from the bowel has been widely questioned, too much evidence which is otherwise unexplainable exists to allow complete abandonment of this hypothesis. Thus, Dorst and Morris¹⁷⁹ attribute the mechanism to a hypersensitiveness of the enteric tract to certain bacteria, most frequently those included under "normal flora." However, quantitative cultural investigation of the stool, including anaerobic methods, will frequently reveal a reversal of the normal quantitative proportions of the intestinal flora (dysbacteria) with a predominance of enterococci or of bacteriologically abnormal colon

¹⁷⁷ MORALES-OTERO P. and GONZALEZ L. M. *Proc Soc Exper Biol & Med* 49: 100 1939

¹⁷⁸ ZINSSER H. and TAMAYA T. *J Exper Med* 44: 753 1926

¹⁷⁹ ARZT L. and FUHS H. *Die Mikroskope Handb d Haut u Geschlechtskr* 11: 602 1928

¹⁸⁰ DORST S. E. and MORRIS, R. S. *Am J M Sc* 180: 650 1930

bacilli. The postulated consequences of this enteric hypersensitiveness is an interference with normal colonic rhythm, possibly constipation, and a train of ensuing physiologic disturbances. Most important of these is the absorption of toxic products resulting from bacterial metabolism. When their concentration is sufficient to overwhelm the detoxifying function of the liver they pass into the general circulation and give rise to various clinical effects. These may include certain types of chronic headaches associated with chronic constipation, cases of "toxic vertigo," and other conditions, in addition to such local intestinal effects as chronic functional diarrheas, and the so-called "irritable or unstable colon" or "neurogenic colitis." This subject is more fully discussed by Urbach and LeWinn.¹⁴²

A number of therapeutic approaches to this problem are available, chief among which may be mentioned diet, the administration of viable colon bacilli, acidophilus milk, and lactose. Morris and Dorst,¹⁴³ Burger,¹⁴⁴ and others believe that sodium ricinoleate (soricin) is capable of detoxifying intestinal organisms and their autolysates, it has also been suggested that it inhibits the action of the proteolytic and putrefactive bacteria upon the contents of the bowel. It is also of value in resistant cases to try autogenous stool vaccines or specially prepared colon bacillus vaccines (Mateer and Baltz¹⁴⁵).

It is proper here to consider the question of hypersensitiveness to viruses. To date very little investigative study has been done on this problem. That sensitization to viruses does occur is shown by the experiments of McKee.¹⁴⁶ Rabbits may be sensitized to the heat-inactivated virus of infectious myxomatosis of rabbits to the point where they give marked wheal reactions to intradermal tests. It has been suggested that the skin manifestations of herpes simplex and of herpes zoster may be of allergic nature, as well as the immune or immediate reaction seen in revaccination for smallpox. The only viral disease in which a skin test is widely employed as a

diagnostic aid is lymphogranuloma venereum. Quite recently, it has been shown that specific dermal reactions may be elicited in persons convalescent from mumps and influenza (Kane¹⁴⁷). The clinical applicability of these reactions in determining susceptibility or immunity to these diseases requires further investigation.

Lastly, the question of the immunologic treatment of bacterial allergies—especially of infectious asthma, sinusitis, and rheumatic diseases—must be given at least brief consideration here. In these conditions—in contrast with the nonbacterial proteinogenous allergies—the terms desensitization (and not merely hyposensitization) or immunization can be properly employed. Furthermore, an increase in the number of antibodies is here desirable and helpful. As to whether it is better to employ autogenous or stock vaccine, the question has not as yet been finally settled. Brown¹⁴⁸ recommends scratch tests with dried bacterial proteins of *Bacillus coli communis* (*Escherichia coli*), *B. diphtheroid* or *pseudodiphtheria* (*Corynebacterium pseudodiphthericum*), *B. Friedlander* or *mucosus capsulatus* (*Klebsiella pneumoniae*), *B. influenzae* (*Hemophilus influenzae*), *B. pertussis* (*Hemophilus pertussis*), and *B. typhosus* (*Eberthella typhosa*), *Micrococcus catarrhalis* (*Neisseria catarrhalis*), *Pneumococcus* (*Diplococcus pneumoniae*) types I, II, and III, *Staphylococcus pyogenes albus*, *S. aureus*, and *S. citreus*, *Streptococcus hemolyticus*, and *S. viridans*. In addition, an occasional patient is tested also with *Bacillus acne* (*Corynebacterium acnes*), *Gonococcus* (*Neisseria gonorrhoeae*), or *Micrococcus meningitidis* (*Neisseria intracellularis*). Readings are made at the end of thirty minutes and again after twenty-four hours, practically all reactions being late ones. The most frequent reactors are *Staphylococcus aureus*, and *Streptococcus hemolyticus* and *viridans*, although the *pneumococcus* and, less frequently, other organisms are at times implicated. Occasionally a reaction is obtained to some organism that cannot be isolated from the patient. This may be explained in some cases by the fact that the infection may be resident in some

¹⁴² MORRIS, R. S., and DORST, S. E. *Ann. Int. Med.* 4: 396, 1930.

¹⁴³ BURGER, G. N. *J. Lab. & Clin. Med.* 19: 234, 1933.

¹⁴⁴ MATEER, J. G., and BALTZ, J. L. *Am. J. Digest. Dis. & Nutrition* 4: 237, 1937.

¹⁴⁵ MCKEE, C. M. *Am. J. Hyg.* 29: 163, 1939.

¹⁴⁶ KANE, L. W. *New England J. Med.* 232: 725, 1945.

¹⁴⁷ BROWN, G. T. *Med. Rec.* July 15, 1941.

inaccessible focus, such as the appendix, or by sensitization resulting from a former infection that has ceased to exist, such as a carbuncle or tonsillitis

The writers are inclined to favor autogenous vaccine, provided it is derived from true foci of infection, and provided it is properly prepared. Kolmer points out that while it is true that a well-prepared stock vaccine may be superior to a poorly prepared autogenous one, a freshly isolated culture is probably antigenically more active than a stock culture that has been grown for a number of generations on an artificial medium. Another reason for the preference for autogenous vaccines is that by employing precisely the same strain of bacteria, one is more likely to achieve a highly specific antibody response, thereby enhancing the patient's immunologic defense forces. Depending on the findings in a given case, cultures may be made from postnasal secretions, sinus contents, throat and gum secretions, sputum, empty stomach contents, bile, duodenal contents, a warm recently passed semiliquid stool, prostatic secretion, urine, and uterine cervix secretions. Naturally, a variety of organisms are obtained in these cultures. Their importance as a causative factor may be checked by the use of complement fixation methods or by the "pathogen selective method" (Solis Cohen¹⁶⁶⁶), in which the autogenous cultures are grown on a medium prepared with the patient's own serum. By the latter means, the nonpathogenic organisms are inhibited and the resulting vaccines are claimed to be particularly effective. According to Lermann,¹⁶⁶⁷ if these methods are not available, a good working rule is that the presence of one or more bacteria in multiple sites in the same patient is an evidence of pathogenicity and an indication for appropriate treatment. Further research with sulfonamide compounds, penicillin, and allied drugs should eventually be of the greatest value in the control of chronic low grade infections, but these agents should not be relied upon to the exclusion of well established surgical and therapeutic principles.

There is a great variation in the dosage of vaccines employed by different authors. The

present writers wish to caution against the all too common practice of beginning tests or treatment with large doses (50,000,000 or 100,000,000 organisms). Such doses frequently bring on severe focal and constitutional reactions. The first dose, which is to be given intracutaneously, should never exceed 1,000,000 organisms. The writers and many others have often found it necessary to reduce the dose to 100,000 and even to 10,000 organisms per injection, because of the severity of the reactions. One is sometimes obliged to repeat the smaller doses for weeks and even months before higher dosage can safely be administered, in such cases, however, the final result is usually very gratifying. In general, the course of vaccine therapy should be extended over many months, and preferably over a period of one to two years. The maximum dosage attained will of course depend on the patient's reactivity, but will rarely exceed 500,000,000 organisms, and will not infrequently fall far short of that figure. In the beginning, the vaccine should be administered once a week, then every two weeks, and finally at monthly intervals.

Regarding the size of the dose, one should be guided by the reaction or effect produced by the last preceding one. The optimal amount is one that results in a local reaction of moderate degree, followed by some amelioration of symptoms. Focal and constitutional reactions should be strictly avoided. A slightly unfavorable response, local or general, is always allowed to subside for a period of a few days before the next dose is given. Systemic reactions are quite infrequent, but may take the form of chills, transitory fever, malaise, headache, and generalized aching.

Stiles et al¹⁶⁶⁸ summarized the possible reasons for failure of bacterial antigen (vaccine) therapy of low grade chronic ("focal") infections as follows:

The cultures may be taken from unsuitable foci. The recovery of organisms of suitable antigenicity may not always coincide with clinical expectations. The cultural procedure may be inadequate from the standpoint of the technique of isolation, the method of selecting the colonies, the incubation period, taxonomic considerations and the methods used to differentiate the etiologic bacteria from the contaminants.

¹⁶⁶⁶ SOLIS COHEN M. Internat Clin 2 214 1939

¹⁶⁶⁷ LERMANN W W. Pennsylvania M J 47 699 1944

¹⁶⁶⁸ STILES M H, BERENS C, RAWLS W B, and CHAPMAN, G H J. Lab & Clin Med 28 1447 1943

The culture selected may not possess suitable antigenic properties. The antigen may be injured during the cultivation process or in later manipulation. The injured antigen may contain an excessive ratio of protein to specific antigen, causing it to be toxic and non-specific.

The dosage may be unsuitable. The injections may be given too often or the amounts may be too large. In other instances the dosage may be too small for adequate stimulation of antibodies. The use of a fixed schedule is condemned.

The condition of the patient may not be favorable for optimum antibody response because of endocrine or nutritional deficiencies, liver dysfunction, an excessive toxic load (e.g., an untreated focus), or other factors.

With regard to the last-named possibility, they point out that numerous patients who reacted badly to small doses of antigen had a beneficial response to much larger doses of the same antigen after foci of infection had been drained or removed. Hence the importance of reducing the toxic load of the body by suitable surgical, chemotherapeutic, or physiotherapeutic measures.

For the treatment of infectious diseases in which bacterial toxins and bacterial antigens are operative—as, for example, in staphylococcus infections—good results can be obtained with preparations that contain both exo- and endotoxins, as well as lysed bacterial proteins. Thus, Sulzberger¹⁶⁵⁹ and Stokes¹⁶⁶⁰ and their associates have reported good results with ambotoxoid (Squibb), and Faust and Etris¹⁶⁶¹ with vatox (National Drug). Similarly, Brown¹⁶⁵⁸ advocates that autogenous heat-killed vaccine organisms be suspended in an unheated Berkefeld filtrate either of the broth in which the same organism had grown for about forty-eight hours, or of saline washings of organisms grown on agar. Such "vaccine-filtrates" contain, theoretically at least, all the proteins, carbohydrates, endotoxins, and soluble toxins within the bacteria or liberated by their growth. Brown¹⁶⁶² achieved excellent results with a filtrate of *Streptococcus hemolyticus* used in asthmatic children over a period of years in conferring the temporary but badly needed immunity in these patients.

In the last few years, oral administration of vaccine and even toxin has attracted a great deal of attention. As early as 1904, Wright attempted oral immunization to typhoid fever with a heat-killed vaccine. Calmette, Beredka, and others performed extensive experiments that finally led to enterovaccination for many infectious diseases, with satisfactory results. According to Dick and Dick,¹⁶⁶³ oral administration of sterile scarlet fever toxin stimulates the body to produce the specific antitoxin in amounts sufficient to change a positive skin reaction to a negative. This subject has been considered at greater length in an earlier section (p. 207).

Recent investigations have centered particularly on oral desensitization to the upper respiratory infections due to pneumococci, streptococci, staphylococci, *Micrococcus catarrhalis*, *Hemophilus influenzae*, Friedlander's bacillus, and other organisms. Although the etiologic agent of the common cold is generally considered to be probably a virus, the identity of which has not yet been established, we have not yet been provided with a prophylactic agent against it. Hence we must attempt to reinforce the individual protective mechanism against the common bacterial respiratory pathogens. These act as secondary invaders as a result either of a lowered general or local resistance on the part of the patient or of an increase in virulence of the bacteria normally present in the upper respiratory tract. Kolmer and Rule,¹⁶⁶⁴ Ross,¹⁶⁶⁵ and other immunologists protected animals against pneumococci by the oral route. In the case of human beings, many authors, including Thomson et al.,¹⁶⁶⁶ Rosenow and Heilmann,¹⁶⁶⁷ Rockwell et al.,¹⁶⁶⁸ and others, reported encouraging results in the prevention of common colds. According to Herron¹⁶⁶⁹ 66 per cent of treated persons developed an immunity to upper respiratory infections. There are avail-

¹⁶⁵⁹ DICK, G. F., and DICK, G. H. *J. Infect. Dis.* 62: 85, 1938.

¹⁶⁶⁰ KOLMER, J. A., and RULE, A. M. *Proc. Soc. Exper. Biol. & Med.* 36, 107, 1932.

¹⁶⁶¹ ROSS, V. *J. Immunol.* 27: 215, 1934.

¹⁶⁶² THOMPSON, D., THOMPSON, R., and THOMPSON, E. T. *Brit. M. J.* 1: 258, 1936.

¹⁶⁶³ ROSENOW, E. C., and HEILMANN, F. R. *Am. J. Clin. Path.* 8, 17, 1938.

¹⁶⁶⁴ ROCKWELL, G. E., LARK, H. C., and POWELL, H. M. *J. Lab. & Clin. Med.* 22: 912, 1937.

¹⁶⁶⁵ HERRON, T. B. *Indust. Med.* 12, 590, 1943.

¹⁶⁵⁸ SULZBERGER, M. B., and REICH, G. *J. Immunol.* 30: 386, 1936.

¹⁶⁵⁹ ANDERSON, L. E., and STOKES, J. H. *Arch. Dermat. & Syph.* 40: 382, 1939.

¹⁶⁶⁰ FAUST, F. B., and ETRIS, S. *J. Immunol.* 46, 313, 1945.

¹⁶⁶¹ BROWN, cited by Forman, *J. Ohio State M. J.* 41: 522, 1945.

able for this purpose various commercial vaccines containing 50 000 million to 60 000 million mixed bacteria commonly found in respiratory infections or in some preparations their water soluble antigenic substances

On the other hand Siegel et al.¹⁷⁰⁶ McGee and his co workers¹⁷⁰¹ and others report that there is no clear evidence that oral or subcutaneous administration of cold vaccines is effective in reducing the number or severity of acute respiratory infections or the incidence of complications. The Councils on Pharmacy and Chemistry and on Industrial Health¹⁷⁰⁷ of the American Medical Association point out that the use of cold vaccines is still experimental and should be under rigidly controlled conditions. Further investigation is essential.

Oral immunization has also been utilized for toxoids. Suitably flavored pastilles containing 100 Lf units of formaldehyde treated diphtheria toxoid were employed by Bousfield.¹⁷⁰⁸ He found that sucking four of the toxoid disks daily for seven days was generally effective in raising the serum antitoxin content in subjects who had a demonstrable amount of antitoxin in the blood or who were definitely known to have reached the Schick negative level at some time in the past. However the method was not suitable for primary immunization. The great value of this treatment is that it can be administered to immune and nonimmune subjects (including adults) impartially without fear of producing local or constitutional reactions.

The intranasal route has also been used for immunization. Application of mixed bacterial vaccines by intranasal spray for prophylaxis of the common cold was attempted by Walsh¹⁷⁰⁴ with encouraging results although Cowan and Diehl¹⁷⁰⁵ were unable to confirm its clinical value. Gold¹⁷⁰⁶ showed that topical application of tetanus toxoid antigen to

the nasal membrane is capable of inducing a rise in antitoxic titer in previously immunized subjects. It may be noted that experimental passive immunization by this route was achieved by Taylor.¹⁷⁰⁷ Immune serum against influenza A virus administered intranasally was much more effective in preventing pulmonary infection with the specific virus than a proportionate amount of the serum injected intraperitoneally.

In cases in which an increase in the number of bacterial antibodies is urgently required it is advisable to perform a so called immunotransfusion. If possible a specific immunotransfusion is preferable in other words a blood transfusion from a donor who has previously had the infectious disease in question. The good prophylactic and therapeutic results achieved with measles and scarlet fever convalescent serum are based on this principle. If time permits specific immunotransfusion may also be performed with blood from donors who have been actively immunized with an autogenous vaccine from the patient. In cases in which convalescent serum is not readily obtainable (for streptococcus for example) it will be found beneficial to use blood from a donor whose leucocyte count has been raised to 10 000 or 12 000 per cubic millimeter by a fever producing injection such as typhoid vaccine (nonspecific immunotransfusion).

2 HYPERSENSITIVENESS TO BACTERIAL TOXINS

In addition to allergy to bacterial protein or carbohydrates there is also a hypersensitivity to bacterial toxins.

A distinction is made between two types of immunologic responses to bacterial toxin. First there are those cases in which the toxin acts as a true antigen and thus evokes the formation of allergic antibodies; this allergy expresses itself in the form of an immediate wheal reaction and the hypersensitivity is passively transferable with blood serum. Until quite recently the very existence of such a thing as a true hypersensitivity to toxin on the basis of an antigen antibody mechanism was the subject of considerable controversy. However, Neill and Fleming¹⁷⁰⁸ succeeded in

¹⁷⁰¹ SIEGEL M, RANDALL M, GIECKER M D and REID M. *Am J M Sc* 205: 681 1943.

¹⁷⁰² MCGEE L C, ANDERSON J E, FLETCHER C A and HAYES S H. *J A M A* 124: 530 1944.

¹⁷⁰³ Report of Council on Pharmacy and Chemistry and Council on Industrial Health. *Indust Hyg* 126: 29 1944.

¹⁷⁰⁴ BOUSFIELD G B. *J M J* 1: 333 194.

¹⁷⁰⁵ WALSH T E. *Ann Otol Rhin & Laryng* 49: 83 1940. *Ch Otolaryng* 34: 1093 1941.

¹⁷⁰⁶ COWAN D W and DIEHL H S. *Ann Otol Rhin & Laryng* 53: 286 1944.

¹⁷⁰⁷ GOLD H. *Am J Su g* 48: 39 1940.

¹⁷⁰⁸ TAYLOR R M. *J Immunol* 41: 43 1942.

¹⁷⁰⁹ NEILL J M and FLEMING G W. *L b d* 17: 419 1929.

sensitizing guinea pigs actively with diphtheria toxin and passively with antitoxic serums, thereby furnishing experimental proof that the primarily toxic antigens possess the same fundamental immunologic properties as do other antigens. Discussing the experimental work of these authors, Zinsser¹¹ agrees in principle with their conclusions (This condition is not to be confused with toxin hypersusceptibility or the *Giftüberempfindlichkeit* of von Behring; see p. 4.)

In general however, bacterial toxin hypersensitiveness is attributable to an underlying toxin-antitoxin mechanism. While bacterial extracts, such as tuberculin, mallein, brucellergen, and trichophyton, indicate the presence of a specific hypersensitiveness in the infected organism by a delayed-inflammatory reaction, bacterial toxin evokes a reaction only in a susceptible individual. This is clearly exemplified by the Schick and the Dick tests for diphtheria and scarlet fever: reactions are positive when the body, either noninfected or in the incubation stage of infection, does not possess a sufficient excess of antitoxin to neutralize the excessive toxin.

The investigations of Koessler, Lewis, and Walker suggest the possibility that bacterial toxins may also play a rôle in allergic conditions such as infectious asthma. These authors succeeded in evoking bronchospasm—in other words, asthmatic attacks—in asthmatics by injecting organisms cultured on bronchial secretions to which histidine and tyrosine had been added. Koessler and his associates, as well as Solis-Cohen,¹⁷⁰⁹ entertain the idea that such attacks may be caused in these cases by bacterial toxins liberated in foci of infection. The important studies of Burky (see p. 135) are also relevant here; he demonstrated that rabbits immunized to staphylococcus toxin also became sensitized to the broth in which the toxin had been produced. Recent observations, both experimental and clinical, have indicated the importance of Staphylococcus toxin liberated from local infectious lesions, as an adjuvant in the development of sensitivity to cutaneous tissues. Thus, by administering increasing doses of Staphylococcus toxoid simultaneously with daily intramuscular injections of minced

rabbit skin, Hecht, Sulzberger, and Weil¹⁷ were able to produce specific sensitization to homologous skin in rabbits. Hopkins and Burky¹⁸ advanced the opinion that certain dermatoses, particularly on the hands, may be due to a similar mechanism: the synergistic effect of toxin liberated by Staphylococci of low-grade virulence growing in the skin leading to local sensitization to epidermal keratin. It should be noted that Burky's animal experiments, which were confirmed by Swift and Schultz, suggest the possibility that bacterial toxins may be a sensitizing factor even in the absence of concurrent hypersensitiveness to the bacterial proteins with which almost all skin tests are performed. In such cases skin tests with vaccines will fail to elicit reactions, since the hypersensitiveness is not in relation to bacterial proteins, there will be positive reactions, however, to tests with toxoid or with toxin-containing culture filtrates.

Although the localized Shwartzman and the generalized Sanarelli-Shwartzman phenomenon are closely related to the question of bacterial toxins, we have seen fit, for certain theoretic reasons, to discuss these phenomena in chapter II.

B. ALLERGY OF INFECTIOUS DISEASES

It is now generally recognized that allergic states and processes are associated with many acute and chronic infectious diseases. However, the writers join Aschoff¹⁷⁰ in rejecting the frequently voiced opinion that infectious diseases are in themselves to be regarded as "allergic diseases." Far more accuracy inheres in the designation "allergizing diseases" (Roessle), indicating that the infectious disease induces a bacterial allergy. Common examples of this type of bacterial allergy are the exanthems in measles, scarlet fever, and typhoid, and certain regularly encountered tissue changes in tuberculosis and syphilis. In addition, there are also parallergic manifestations; that is, in some instances, concomitantly with the normal symptoms of the infectious allergy (e.g., an exanthem), the disease may give rise to other clinical syndromes. For example, acute nephritis complicating scarlatina is considered as a parallergic phe-

¹⁷⁰⁹ SOLIS-COHEN, J. *J. M. World* 60: 433, 1947

¹⁷⁰ ASCHOFF, L. *Med. Klin.* 31: 1, 1935.

nomenon (p 26) as are also some forms of asthma following tuberculosis (tuberculo allergic asthma)

Pathogenetically the clinical manifestations of almost all infectious diseases may be attributed to three factors the importance and effect of which differ greatly in various cases and in the several stages of the same disease (1) the specific affinity of the bacteria for certain organs or tissues (e.g. predilection of the typhoid bacillus for the lymphatic tissue of the small intestine) (2) the influence of the toxic components of the micro-organism (3) the hypersensitiveness resulting from allergization of the body by the invading micro-organisms or their products of growth This last factor is naturally the only one to be discussed here

Von Pirquet¹ was the first to call attention to the similarity between many of the clinical manifestations of acute infectious diseases and those of serum sickness or experimental anaphylaxis Such manifestations include an incubation period of about eight to ten days followed by the appearance of an exanthem and characterized by regularity of the course cyclic behavior and the like Von Pirquet expressed a view that was at the time nothing short of revolutionary—namely that the incubation period actually represents not merely the time during which the infectious agent multiplies but rather the interval necessary for the formation of antibodies to the bacterial protein He suggested in other words that the onset of most infectious diseases is attributable to the reaction between the antibodies and the greatly increased number of invading bacteria and that the transitory exanthems of such diseases as measles and scarlet fever correspond to serum exanthems and the critical drop in temperature to that in anaphylactic shock Friedberger attempted to explain *all* the manifestations of infectious diseases as anaphylactic processes thus eliminating the necessity for assigning bacterial endotoxins and exotoxins any part whatsoever This extreme view must of course be promptly rejected

As mentioned above the conditions determining the course of an infectious disease are complicated by the fact that several—and to a great extent independent—factors bring

their influence to bear Probably the most important of these as repeatedly emphasized by Cannon (see chap X) is an adequate protein metabolism Depletion of protein reserves due to such causes as starvation chronic disease or severe proteinuria and reflected in a state of hypoproteinemia is associated with a loss of resistance to infection Nitrogenous nutriment tends to restore the integrity of the antibody mechanism and favors the formation of phagocytic cells in the bone marrow as a result the processes both of acquired immunity and of natural resistance are enabled to function more effectively Furthermore it must be remembered that the micro-organisms are constantly multiplying with the result that the quantitative relationship between antigen and antibody is continually fluctuating Nevertheless the interpretation of many of the various manifestations as allergic appears to be warranted at least to a certain extent This will be discussed in some detail below in relation to each disease

Since it is true that in non fatal acute infectious diseases the microbes are finally and completely destroyed by the ever increasing effectiveness of the antibody mechanism the bacterial allergy of these diseases always runs a course of three definite phases of allergization and these phases develop in a regular order (Riehm¹²⁰) When the organism possesses a small supply of antibodies—as at the time of the first infection and shortly thereafter—there are no manifestations of hypersensitiveness During this time the micro organisms multiply without restraint (incubation period) This is followed by a period in which the bacterial antigens are bound by the tissue antibodies At this time the inflammatory disease manifestations begin to appear—in the form for example of exanthems (disease stage) In this second phase however the bacterial invasion is usually conquered by extermination of the microbes with the result that the quantity of antigen in the organism reverts to zero This is followed by the third phase during which only antibodies are present in the organism This period is also marked by an absence of clinical manifestations nor does the disease picture reappear on eventual reinfection due to the relatively

small number of bacteria, because the great supply of antibodies readily prevents multiplication of the micro-organisms and thereby an increase of the bacterial antigen. Like the first phase, then, the third runs its course without manifest symptoms, and is in fact apparent only on deliberate administration of the bacterial antigen—as, for example, in skin testing. Hence it is called the stage of immunity. At least theoretically this immunity is only relative, but it is generally sufficient to combat the small number of bacteria involved in a spontaneous reinfection.

In the bacterial allergy of the chronic infectious diseases (tuberculosis, syphilis, etc.) conditions are somewhat different; this is due to the fact that the micro-organisms cannot be destroyed all at once, even when the tissues are abundantly supplied with antibodies. Hence, the infectious agent can continue to exist for prolonged periods of time at certain sites in the tissues. An increase in the supply of antibodies, therefore, merely inhibits the multiplication of the micro-organisms; but this eventually brings about a decrease in the quantity of the antigen. Here again we are dealing with a phase of immunity, but one in which the spontaneous inflammatory-allergic disease manifestations retrogress. However, when for some reason there is a decline in the antibody titer, or when it is lowered by some intercurrent episode, the micro-organisms immediately begin to multiply or metastasize. Thus, there is an immediate and rapid increase in the quantity of antigen, leading to the reappearance of inflammatory-allergic manifestations—to a relapse, in short—characterized by a number of separate waves of symptoms.

Thus, in chronic infectious diseases it is possible, under certain circumstances, for a case of bacterial allergy to run a course marked by alternating phases of manifest disease and of immunity. This applies equally to the disease itself and to local manifestations of immunity. The expression of this phasic alternation of local hypersensitiveness and relative immunity takes the form of annular, circinate, serpiginous, polycyclic, and corymbiform lesions of the skin, all of which are commonly observed in chronic infectious diseases such as syphilis, tuberculosis, and dermatomycoses (FIG. 224). The actual existence

of this specific acquired local resistance, following in the wake of specific sensitivity, was demonstrated by the experimental superinoculations performed by Epstein.¹⁷¹¹

Naturally, the phases of immunity are only relative. The degree of immunity does, as a rule, suffice to cope with superinfections coming from without and usually involving a relatively small number of bacilli—as in tuberculosis, for instance. But the immunity is unable to deal with the massive superinfections that result when a local abscess breaks into one of the body cavities, for example, or into a bronchus. In these instances the antibody mechanism appears to be overwhelmed by the massive assault of bacilli. However,



FIG. 224 TRICHOPHYTOSIS PERIPHERAL EXTENSION AND CENTRAL HEALING, CHARACTERISTIC OF SUCCESSIVE STAGES OF INFECTION AND IMMUNITY

the success or failure of the micro-organisms in infecting these new sites depends upon the balance between the number of organisms and the opposing antibodies.

The influence of this mutual relationship between the antibodies and the bacteria becomes clearer when the spread of the infection proceeds hematogenously. When there is a considerable excess of the former, the entrance of the bacilli into the blood stream occurs without evoking any symptoms. When the supply of antibodies is somewhat smaller, the abrupt hematogenous shower can, under certain conditions, produce disease manifestations restricted to one system—for example, isolated tuberculosis of a single organ. When

¹⁷¹¹ EPSTEIN, S. J. Invest. Dermat. 3, 223, 1940

the antibody supply is relatively inadequate the momentary hematogenous assault brings on simultaneous disease manifestations in a number of organs—as for example in generalized miliary tuberculosis

In conclusion let us briefly consider the bearing of the infected organism's level of immunity of the course of the disease and on the development of the various allergic syndromes. The same micro organisms will (1) in the absence of immunity after an incubation period cause a rapidly progressing fatal disease (2) in the presence of a moderate degree of immunity produce a reaction immediately following the reinjection with extensive organ involvement at first appearing to be very severe but characterized by a tendency to ultimate healing (3) in the presence of strong immunity bring about the prompt destruction of the disease agents and thus prevent their spread

However when there are frequent or repeated invasions by such bacteria as streptococci and pneumococci they result in reactive destructive lesions that have been designated as rheumatoid diseases. These conditions generally involve the endocardium and the joints occasionally also the kidneys regardless of which particular organism is responsible. In other words the nature of the infecting micro organism is apparently of less importance in the production of the given allergic disease picture than is the individual's state of immunity at the time. The clinical recognition of the significance of the degree of immunity of the infected host dates back to the so called fundamental experiment by Robert Koch (see p 457) which basically applies to all infectious diseases

The first histologic verification of this principle was contributed by J Jadassohn^{17 2} and Lewandowsky^{17 3} (so-called Jadassohn-Lewandowsky law). These two authors showed that when bacteria are able to multiply without restraint within the body (owing to the absence of immunity) the host responds with a nonspecific banal inflammatory reaction but that when on the other hand bacteria or their products enter into reaction with antibodies (owing to the existence of a more or less

strongly developed immunity) the result is the formation of tubercles or of tuberculous structures not only in tuberculosis but in all inflammatory processes of bacterial allergic origin. On the basis of this law it may now be said with assurance that when tuberculous structures appear in the course of an infectious disease it can be assumed that under the influence of antibodies the micro organisms are undergoing disintegration and are being gradually eliminated in that site

The relationship between the various acute and chronic infectious diseases and their bacterial allergic manifestations will be briefly considered below. For a more detailed discussion of this subject the reader is referred to Kolmer and Tuft's^{17 4} excellent contribution *Clinical Immunology*. The diagnostic value and limitations of skin tests in various bacterial and viral diseases were recently reviewed by Kane.^{18 1}

C ACUTE INFECTIOUS DISEASES

I STAPHYLOCOCCUS INFECTIONS

In evaluating the skin reactions to staphylococcal extracts one must differentiate between the filtrates of staphylococcal cultures that are active because of their toxin content and staphylococcal vaccines that represent bacterial protein or carbohydrates

The intradermal response to dilute staphylococcal toxin is often positive in healthy individuals (Greenbaum-Harkins) while it is usually negative in subjects who have or have had a staphylococcal skin disease. This could be explained by the theory that the toxin is neutralized by the antitoxin formed during the infection. However these findings are not constant. M. Neisser and Sulzberger and Rubin have reported positive skin reactions in individuals whose serum contained a high antitoxin titer

As a result of these confusing and unpredictable findings many authors have chosen to forego testing with culture filtrates (bacterial toxins) and to perform their tests with bacterial vaccines or with dry extracts of bacterial protein (Frei-Hajós). It is also interesting to note the results obtained by Riviere and by Francis and Tillet on skin

^{17 1} JADASSOHN J. *Arch Dermatol Syph* 119: 10, 1914

^{17 2} LEWANDOWSKY F. *De Tuberkulose der Haut*. Berlin: Springer, 1916

^{17 4} KOLMER J A and TUFT L. *Clinical Immunology*. Boston: and Chemotherapy Philadelphia: Saunders, 1941

testing with specific bacterial polysaccharides. Riviere demonstrated that the antigenic activity of vaccine is diminished by hydrolytic cleavage of these polysaccharides in the bacterial suspension.

Many authors, including the present writers, have obtained satisfactory results with bacterial vaccines. As a preliminary step, intradermal tests must be performed on clinically healthy individuals to determine how many organisms can be administered without eliciting a local reaction, this dose should then be used for testing patients. With our strains we generally feel justified in considering positive skin reactions to 5,000,000 staphylococci or to 3,000,000 streptococci (contained in 0.1 cc.) as specific allergic responses. In small

Analogously with the tuberculids and phytids, the microbids (staphylo- and streptococoids) are to be regarded as the characteristic allergic response. This means that hematogenously borne specific micro-organisms can evoke papular, lichenoid, or bullous lesions in the allergized skin as an expression of the antigen-antibody reaction in this tissue (E. Hoffmann, Schreus).

The concept that staphylodermas may be due either to toxin effects or to sensitization to the proteins or carbohydrates of the micro-organisms, or to a combination of both, has led to the attempts to use the so-called ambotoxoids (FIG. 225), which combine the toxic as well as the bacterial principles (see p. 411), and which, it is hoped, may effect a higher

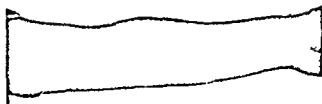


FIG. 225. REACTION TO STAPHYLOCOCCUS AMBOTOXOID (0.1 CC. OF 1:100 DILUTION) IN CASE OF SICOSIS BARBAE

children, the corresponding figures are approximately 1,000,000 staphylococci and 300,000 streptococci.

It is occasionally observed that positive reactions are elicited only by one particular species of staphylococcus—most commonly by *Staph aureus haemolyticus*, but sometimes by *Staph. albus*, and rarely by *Staph. citreus*. In some instances the patient will react only to autogenous vaccines.

It is far more difficult to demonstrate the presence of a bacterial allergy by means of skin tests in a so-called focal infection. This term in its broadest sense designates the ability of a localized bacterial infection to exert a pathologic influence on tissues far distant from the actual site of the disease—a process capable of exerting a considerable effect on the immunologic state of the entire organism. Cutaneous reactions are most likely to be elicited under these conditions by employing autogenous vaccines.

degree of the desirable anti-bacterial as well as antitoxic immunity.

2. STREPTOCOCCUS INFECTIONS

Here too, diseases or manifestations produced by streptococci are based on two mechanisms that may be operative either alone or in combination with each other: (1) toxin effects, and (2) sensitization with nontoxic products, i.e., to the streptococcic antigens. Differentiation of these effects may be attempted by testing the reactivity of the skin to streptococcic toxin and streptococcus vaccine. If there is a toxin hypersensitiveness, the infected organism fails to react, for example, to scarlatina toxin (Dick test); on the other hand, when the patient is sensitized to the streptococcic antigen, skin reactions to the vaccine will be positive. It must be borne in mind, however, with regard to both toxins and bacterial antigens, that some patients will react only to a particular strain,

thus making it desirable to use autogenous filtrates and vaccines if possible. It is not permissible, therefore, to draw any conclusions—either in the positive or in the negative sense—from the results of tests performed with only one strain of streptococcus, regardless of its potency, for even in the same individual different strains are capable of evoking utterly dissimilar responses on skin testing. Furthermore, it should be noted that the skin can react metallurgically—as shown, for example, by the reactions to bacterial filtrates observed in tuberculin positive but otherwise noninfected children (p. 28).

As for the immunologic state in human beings, Derick and Fulton have shown that healthy children up to the age of 5 years only exceptionally give positive skin reactions to streptococcus vaccine, however, as the individual advances in age, he becomes more and more likely to respond with a positive reaction to such a test. This is probably the result of bacterial infections, evidence of a moderate degree of skin hypersensitiveness is, therefore, hardly of any practical diagnostic significance. Nevertheless when the response to such a test is quite marked and especially when it is accompanied by focal and constitutional symptoms, it may be considered as evidence of a specific hypersensitiveness.

SCARLET FEVER (SCARLATINA)

There are two schools of thought: one explains all the symptoms of scarlet fever, with the exception of the septic complications, on the basis of the direct action of the toxins, without the participation of an allergic mechanism (Hooker, Kolmer and Tuft, Zinsser, and others); the other view is that the rash of scarlet fever is to be interpreted as an allergic manifestation attributable to the toxin circulating in the blood (Schick, Bristol, Cooke, Dochez et al., and others). The latter concept is based on the experimental evidence that animals can be sensitized with beta hemolytic streptococcus cultures, as well as with filtrates comprising the so-called "Dick toxin," and that these antigens can be neutralized by antiscarlatinal serum.

Meyer and Schlossmann have attempted to explain the fact that scarlet fever expresses itself in such a variety of symptoms as the

result of the varying allergic reactivity in different individuals—and not on the basis of hypothetical fluctuations in virulence on the part of the micro organism.

Special mention must be made here of the skin test with scarlet fever streptococcal toxin—the Dick test.

TECHNIC. Precisely 0.1 cc. of the Dick test toxin is injected intracutaneously and for a control, the same quantity of a toxin previously heated to a temperature of 120° C. and thus freed of its specific toxicity. The reaction is to be interpreted as positive when a red area about 1 to 3 cm. in diameter appears within eighteen to twenty-four hours after the injection while the site of the control injection with the heated toxin manifests either no response at all or only a very faint one. Pseudoreactions occasionally observed can be recognized by the fact that they fail to regress within two or three days and are probably due to hypersensitiveness to streptococcus protein which is likewise contained in the control injection.

Individuals who have never had scarlet fever nor been immunized to it generally respond to the test with a positive reaction. It must be added, however, that an appreciable percentage of individuals in this group fails to react; furthermore, a positive skin reaction in action indicates only that the individual in question may acquire the disease, but will not necessarily. Thus, of the asymptomatic carriers of the strain of *Streptococcus* responsible for a scarlet fever epidemic in Rumania there were as many Dick positive reactors as Dick negative (Schwentker et al.¹⁷¹³). Moreover, American Indians, who possess a natural immunity to scarlet fever, nevertheless frequently give positive reactions to the Dick test. Furthermore, it has been reported that positive Dick test reactions were given by persons who had had scarlet fever. But of course the great majority of such individuals fail to react to the test. A negative Dick test may generally be accepted as an indication that the subject is immune to scarlet fever—the immunity being attributable to the presence of antitoxins in the blood.

The practical diagnostic value of this test is somewhat decreased, however, by the fact that the reaction, although definitely positive before the onset of scarlet fever, may become

¹⁷¹³ SCHWENTKER, F. F., JANNEY, J. H. and GORDON, J. E. *Am. J. Hyg.* 38: 27, 1943.

negative during the first forty-eight hours of the disease. Grossmann points out that children with active tuberculosis are far more likely to be Dick-negative than other children of the same age—that is, tuberculosis tends to weaken the Dick reaction. Thus, it has occasionally been observed that a Dick-positive tuberculous child becomes Dick-negative without having scarlet fever. For all these reasons, many authorities have begun to lose confidence in the scarlet fever test. Opinions are still sharply divided, however, and this is probably due to the fact that in hypersensitiveness to scarlet fever toxin, as in all states of hypersensitiveness, there is no absolute parallelism between the hypersensitiveness of the skin and that of the organism as a whole. In some children, for example, the Dick test elicits a definite reaction, but administration of the toxin subcutaneously or intramuscularly evokes no manifest response. Therefore, whenever the circumstances in a given case appear to cast doubt on the validity of the Dick concept, such a general toxin test should be performed. And, despite all theoretic objections, it is certainly advisable actively to immunize all Dick-positive individuals with scarlet fever toxin when there is known danger of exposure.

The presence of scarlet fever antitoxins seems to account not only for failure to react to the Dick test, but also for the blanching phenomenon (rash extinction test) of Schultz-Charlton.

TECHNIC. The phenomenon denotes that it is possible to make the scarlet fever exanthem disappear locally by the intracutaneous injection of 0.5 cc. of normal human serum or of serum taken from persons convalescing from scarlet fever, but not before the twentieth day of the disease. Diluted animal antitoxic serum, provided the patient is not serum sensitive, or placental immune globulin may be used similarly in doses of 0.2 cc. Neither autogenous serum nor serum from persons with active scarlet fever is capable of causing the lesions to fade. The injection is made in an area of bright red rash. In a positive test, local blanching usually begins to appear after six or eight hours.

This phenomenon is of practical diagnostic value in two ways. (1) An exanthem that is made to disappear by means of duly tested serum is thereby proved to be a symptom of scarlet fever, while an exanthem that does

not respond in this manner is not an expression of this disease. However, there are definite limitations to the use of the rash extinction test in the diagnosis of scarlet fever. The absence of a positive reaction does not negate the diagnosis and its value diminishes progressively with the aging of the rash. Moreover, in some rare instances, the cutaneous lesions of measles, varicella, and syphilis are also blanched by this procedure. (2) A patient does not have scarlet fever if his serum, taken within the first three weeks of his illness, causes a proved scarlet fever exanthem to blanch.

It should be borne in mind that the Schultz-Charlton phenomenon has none of the clinical or serologic earmarks of an allergic reaction. It is in all probability due to local antitoxin action.

The occurrence of sensitivity to the hemolytic streptococcus itself is suggested by the observations of Conner and Milzer.¹⁷¹⁶ They studied three patients who developed urticaria with elevated temperature appearing during the course of uncomplicated scarlet fever eight to twenty-six days after its onset. Positive reactions were consistently obtained on skin testing with bacterial suspensions isolated from their throats, while heated and unheated Berkefeld filtrates, Dick toxin, and human convalescent serum gave no reactions. One patient had a mild urticaria with his second attack of scarlet fever and a severe one with his third. These authors present the possibility of bacterial allergy as a cause of this complication, as well as the possibility of correlation of streptococcus allergy to delayed or late hemorrhagic nephritis and nonsuppurative arthritis. Goodall and Washbourn¹⁷¹⁷ had earlier described an uncommon secondary rash appearing during the second or third week of scarlet fever and distinct from the punctate erythema present at the onset. They called attention to the close resemblance of this to the urticarial eruption following the injection of therapeutic serum. These findings appear analogous to the animal experiments of Derick and Swift,¹⁷¹⁸ who observed a secondary skin

¹⁷¹⁶ CONNER, J. A., and MILZER, A. *Illnesses* M J 84, 214, 1943

¹⁷¹⁷ GOODALL, E. W., and WASHBOURN, J. W. *Textbook of Infectious Diseases* 3d ed. London H K Lewis & Co., 1928, pp. 4, 262

¹⁷¹⁸ DERICK, C. L., and SWIFT, H. F. *J. Exper. Med.* 49: 615, 1929

reaction at the primary site of inoculation in rabbits intracutaneously injected with non hemolytic streptococci about ten days previously. Coincident with the appearance of this secondary reaction the rabbits were hypersensitive to the inoculated streptococci and exhibited cutaneous corneal and toxic reactions similar to those produced by tuberculin. These workers believe that a sufficient amount of residual antigen persists at the site of inoculation to react and cause a recurrence of acute inflammation when the animal has developed hypersensitiveness as the result of the original injection.

3 MEASLES

In the opinion of the majority of authors the exanthem in measles is—unlike the exanthem in scarlet fever—the direct result of infection. This view is maintained in spite of the fact that many questions as to the nature of the causal agent have not as yet been conclusively answered although it is generally supposed to be a virus. It is interesting to note that no less an authority than von Pirquet¹⁷¹³ first advanced the opinion—based on clinical observations and comparisons particularly of variola and vaccination—that the regular course of the measles eruption is to be regarded as the expression of an allergic response to the causative agent of measles. Hecht¹⁷²⁰ later tried to explain the second rash in measles by interpreting it as the result of an awakening of the organism's reactivity (after the expiration of the anergic period that is so characteristic of measles) rather than as a mere sequel to measles. This view was based on the observation that the second rash appears on the tenth day after the initial exanthem and sometimes recurs on the eighteenth day of the disease.

Ever since Preitsch called attention to the fact, it has become widely known that an individual who has previously given positive reactions to tuberculin will often fail to respond to a tuberculin test performed during the eruptive stage of measles (parallergic hypersensitiveness see p. 27). On the basis of exhaustive investigation von Pirquet reported

that the tuberculin papule ceases to become palpable three days prior to the appearance of the exanthem; that on the day of the eruption and during the next seventy-two hours it is impossible to perceive any reaction whatsoever and that not until the ninth day is the former state of cutaneous hypersensitiveness to tuberculin restored. Analogous conditions prevail with regard to skin tests with cowpox lymph and trichophyton during the eruptive stage of measles. On the other hand tests performed with toxins as in the Dick and the Schick test frequently elicit more strongly positive reactions during and following an attack of measles.

4 DIPHTHERIA

In diphtheria the clinical immunologic manifestations are confined to cutaneous hypersensitiveness as ascertained by testing with the specific toxin. This is the basis of the well known Schick test which has a double purpose: (1) to determine susceptibility to diphtheria, (2) to prove whether prophylactic inoculation has produced the desired state of immunity.

TECHNIC. Precisely 0.1 cc. of diluted toxin containing one-fiftieth of the minimal lethal dose for the guinea pig is injected intracutaneously. The reaction may be considered positive when it presents a distinct area of erythema, edema, and induration that is definitely larger than that presented by the control and when this area exceeds 10 mm. in diameter. The reaction appears after twenty-four to ninety-six hours and attains its maximum on the fifth to seventh day after the injection. For the control heated diphtheria toxin is injected into the opposite arm. When the latter injection also elicits local skin manifestations the response is to be regarded as a pseudoreaction attributable to hypersensitiveness to a substance other than diphtheria toxin. The provocative substance may consist either of diphtheria proteins (as the result of an acquired allergy to the bacterial products) or possibly of the peptone now commonly used for culturing the bacillus in the preparation of the toxin or as a buffer diluent. A pseudoreaction has the same clinical significance as a negative reaction. The manifestations of pure pseudoreactions begin to fade after four days while as mentioned the manifestations of a true diphtheria reaction persist for a longer time. In addition a combined reaction may occur but can be recognized by the fact that the control test fades before the true reaction reaches its height. It is generally held to indicate susceptibility to diphtheria as well as sensitivity to diphtheria bacillus protein.

The Schick test fails to elicit a reaction when immunization has been achieved or when the

¹⁷¹³ PIRQUET, C. F. von. *Ztschr. f. Kinderh.* 6: 1, 1913.

¹⁷²⁰ HECHT, A. F. *ibid.* 43: 149, 1927. *Wien. klin. Wchnschr.* 40: 1097, 1927.

individual has recovered from the disease, or is otherwise immune.

A positive reaction to the Schick test is supposed to indicate that the individual does not possess a sufficient antitoxin titer to insure adequate protection against the disease, that is, the individual is susceptible to infection with diphtheria. In some instances, however, an individual whose blood contains an adequate supply of antitoxin will give a positive reaction to this test. In general, failure to react may be accepted, with certain reservations, as an indication of the presence of antitoxin. It must be stressed, however, that in severe septic cases there is likewise no reaction, although there are no protective bodies in the blood. The same is true of cachectic individuals and newborn infants.

Although the combined reaction usually indicates susceptibility, recent experience suggests that many such subjects may actually be immune to diphtheria. Moreover, these persons are exceedingly likely to manifest untoward reactions to toxin-antitoxin mixtures or to toxoid, and should be immunized cautiously, if at all. (The oral method of Bousfield¹⁷²³ may be of value under these circumstances.) In doubtful cases, a decision can be made on the basis of determinations of the serum antitoxin titer.

Systemic reactions to immunization with diphtheria toxoid are most frequent and severe in persons who are immune to diphtheria. Hence it is essential that they are recognized and not treated.

A test with 0.1 cc. of a 1:100 dilution of toxoid injected intradermally into the volar surface of the forearm, known as the Moloney¹⁷²⁴ test, should be performed on all Schick-positive subjects over the age of 5 who are to be immunized (Underwood¹⁷²⁵). A positive reaction consists of an area of erythema greater than 1 cm. in diameter present at the end of twenty-four or forty-eight hours. If the Moloney test indicates sensitivity to bacterial protein, the immunization may be carried out with divided dosage.

In cutaneous diphtheria, the Schick test sometimes fails to elicit a reaction even in the

unaffected sites, while in a certain number of other cases, one encounters only local immunity—in other words, positive reactions occur only in unaffected skin sites. This may well be due to the fact that the skin infection is unable to produce a sufficient quantity of antitoxin to provide for the immunization for the entire skin surface. Another possible explanation is that the reactions fail to appear because the skin tests are performed too soon—i.e., before the antitoxin has had time to be generally distributed.

The failure of the Schick test to elicit a reaction in a given case is merely an indication of an adequate titer of antitoxins in the blood, and in no way refers to the presence of antibacterial immune bodies. The reactions to the latter take two forms: the delayed-inflammatory type as in the pseudoreaction, described above, and the immediate-urticarial type observed by Neill and his associates.¹⁷⁰³ These authors were actually able to achieve passive transfer of the hypersensitiveness to diphtheria antigen by means of these antibodies, employing the Prausnitz-Kuestner technic. Here, as in all the other diseases in which both types of reaction (delayed-inflammatory and immediate wheal) are observed to appear concurrently, the relationship between them has been insufficiently studied.

According to Chiari and Siegl, allergization of individuals suffering from diphtheria is caused, in the great majority of cases, by the protein of the diphtheria bacillus. This allergization attains its maximum at the end of the first week or some time during the second week of the illness, and can be recognized by the so-called pseudoreaction.

The literature contains a few isolated reports (Monroe and Volk,¹⁷²³ Bousfield¹⁷²⁴) showing that individuals may become highly allergized by the protein of the diphtheria bacilli during the course of the disease, and that repeatedly performed Schick tests can, in such cases, evoke anaphylactic reactions. Parish¹⁷²⁵ collected 7 cases of this kind from the literature and added the same number from his own material. In 2 of these cases the

¹⁷²³ MOLONEY, F. J., and FRASER, C. J. *Am. J. Pub. Health* 6: 1077, 1927.

¹⁷²⁵ UNDERWOOD, E. A. *J. Hyg.* 35: 449, 1935.

¹⁷²⁴ MONROE, J. D., and VOLK, V. K. *Am. J. Pub. Health* 24: 342, 1934.

¹⁷²³ BOUSFIELD, G. *SI. Officer* 56: 193, 1936.

¹⁷²⁵ PARISH, H. *J. Larcet* 2: 319, 1935.

anaphylactic symptoms were found to be due to hypersensitiveness to the Witte peptone that had been used in the preparation of the toxin. While this may be the explanation in some instances the painstaking animal experiments of Neill Sugg and Richardson^{17, 18} proved that experimental anaphylaxis can be induced in guinea pigs by diphtheria toxin or toxoid serving as the antigen with antitoxin as the antibody in the reaction. In human beings immediate allergic reactions to diphtheria toxin are very rare but Beck¹⁷⁷ observed 3 instances in a series of 15 726 Schick tests.

Finally it is interesting to note the observation of Siegl¹⁷⁸ that the injection of diphtheria toxoid is sometimes followed within a few days by the appearance of large maculopapular exanthems on those skin areas to which Loewenstein's prophylactic toxoid containing ointment has been applied. According to Siegl these manifestations are to be interpreted as flare up phenomena and indicate active immunization resulting from the protective inoculation.

All these investigations make it clear that one can no longer doubt the existence of a specific allergy to the diphtheria bacillus following prophylactic immunization or active disease.

5 PNEUMOCOCCAL INFECTIONS

The observations reported by Avery and Heidelberger have shown that the determinant of type specificity of the various pneumococci is the carbohydrate hapten which is different for each type of pneumococcus while the determinant of species specificity is the protein of the bacillus.

As to the immunologic response of the skin in pneumococcal infections the conditions are very similar to those observed in diphtheria. Extracts containing toxin elicit skin manifestations only in healthy individuals. On the other hand bacterial antigens evoke positive reactions in individuals who have recovered from pneumococcal disease. The positive response is of the immediate wheal

type when the polysaccharides of the pneumococci are employed; this reaction is type specific. It has been of value as a guide to serum therapy and as a prognostic aid. But when the pneumococcus protein is used for skin testing a delayed inflammatory reaction is obtained that is not type specific (Tillet and Francis).

6 PERTUSSIS

For skin testing Streat⁷²⁹ recommends the use of 0.1 cc. of a 1:600 dilution of the endotoxin derived from *Haemophilus pertussis*. A positive reaction is to be interpreted as an indication of susceptibility to this disease. This test thus bears the same immunologic relationship to pertussis as the Schick test does to diphtheria. The skin test must be kept under close observation between the seventh and twenty-fourth hours for the appearance of erythema, since this manifestation may be transient. Opinion is still divided regarding the merits of this test. Thus Kuntler¹⁷³⁰ found it to be a reliable index of immunity to pertussis while Silverthorne, Fraser and Brown¹⁷³¹ report it to be of no value. Flosdorf et al.¹⁷³² had encouraging results with the detoxified antigen or so called agglutinin prepared from *Haemophilus pertussis* but further study is necessary.

7 TYPHUS

With the use of an extract of *Proteus X₁₉* (Exanthum) Fleck and Heschles¹⁷³³ as well as Nemschulov have perfected a skin test for typhus. This procedure which is analogous to the Dick and Schick tests elicits a definite reaction in healthy individuals while no cutaneous response is observed in typhus patients or in individuals who have had the disease within the preceding four years.

8 VARIOLA AND VACCINIA

Ever since the time of Jenner (1796) cutaneous vaccination with cowpox virus has

¹⁷² NEILL, J. M., SUGG, J. Y. and RICHARDSON, L. V. *J. Immunol.* 19: 109, 1930.

¹⁷³ BECK, J. R. *Delaware State M. J.* 13: 25, 1941.

¹⁷⁴ SIEGL, J. A. *Ch. I. K.* 103: 223, 1934.

⁷²⁹ STREAT, L. P. *Campd. M. A. J.* 42: 535, 1940.

¹⁷³⁰ KUNTLER, M. *ibid.* 52: 62, 1941.

¹⁷³¹ SILVERTHORNE, N., FRASER, T. and BROWN, A. *ibid.* 50: 129, 1944.

¹⁷³² FLOSDORF, E. W., FELTON, H. M., BONDI, A. JR. and MCGO, N. *NESS, A. C. Am. J. M. Sc.* 206: 432, 1943.

¹⁷³³ FLECK, L. and HESCHLES, I. *Klin. W. hnschr.* 10: 107, 1931.

been widely and successfully used for immunization against smallpox. This reaction of an organism to the first vaccination differs greatly from that of an organism subjected to revaccination. The altered reactivity is here basically similar to that induced by a second injection of foreign serum, or by reinoculation with living tubercle bacilli, in animals previously infected with tuberculosis (Koch's experiment). Von Pirquet's concept of allergy was based on observation of the phenomena of vaccination and revaccination, as well as of serum sickness and tuberculin hypersensitiveness.

The following three types of vaccinal skin reactions are observed:

(1) The immune reaction, sometimes called the immediate reaction. This consists of a macule or papule—never a pustule—and a small areola, appearing in about twelve hours and lasting for forty-eight to seventy-two hours. The subcutaneous induration is readily palpable at the vaccination site. This type of reaction is a clear evidence of immunity to smallpox and is to be classified as a positive energy. It is often overlooked, usually through failure to examine the vaccination site at the proper time, and is therefore often reported as "negative" or a failure to "take." However, there is widespread agreement that a complete lack of reaction to vaccination can be due only to the use of an impotent or deteriorated vaccine, or of a faulty technic, and hence is an indication for revaccination with particular care.

(2) Vaccinoid or the accelerated reaction. This goes through the same stages as a primary vaccination, but the entire process is condensed into a period of a few days, reaching its height on the sixth or seventh day. However, the local reactions are much smaller, and there is very seldom any malaise or fever. This reaction is evidence of a partial immunity from a previous attack of smallpox or a previous vaccination. The accelerated reaction is the basis of Hooker's¹⁷⁴ skin test with killed vaccine virus, to determine whether or not the individual is susceptible to smallpox. Absence to a reaction to this test is interpreted as a definite indication for revaccination. This test also permits an evaluation of the degree

of immunity; since it is performed without the use of living virus, the procedure is particularly advantageous in cases of dermatitis, and also when it is desired to ascertain the degree of the patient's resistance to smallpox, without subjecting him to vaccination.

(3) Primary vaccinia or primary "take." This occurs in those who have never had smallpox or been previously vaccinated, or who have lost their immunity. The rapidity and severity of the reaction may be modified slightly by some degree of retained immunity.

In addition, Regan¹⁷⁵ has recently described another type of immediate reaction—not to be confused with the immune reaction above—occurring only on primary vaccination and only if the vaccination will subsequently "take." It consists of a minute blanched zone appearing almost immediately (within three to ten minutes) and quickly developing into a minute white papule with a faint surrounding erythema. The papule is at the border of ordinary visibility and may require magnification, it persists for about twenty minutes. This is a rediscovery of the observation of Cohen¹⁷⁶

Davidson and Davis¹⁷⁷ considered the possible association of allergy and postvaccinal reactions. They reported four patients, all of whom had a personal or family history of allergy, with unusual reactions eight to ten days after vaccination. Purpuric lesions and angioneurotic edema appeared in two cases, and purpura alone and generalized vaccinia in the others.

A number of immunologic methods are available for the diagnosis of smallpox. The most important is the procedure contributed by Tièche¹⁷⁸; in doubtful cases of variola, the contents of a fresh pustule from the patient are sterilized by heat and then injected intracutaneously into a subject previously immunized, by numerous vaccinations, to vaccinia and consequently to smallpox. If the case is one of variola (or vaccinia) a characteristic early reaction begins to develop after four hours. Since such multiple-vaccinated subjects are rarely available, Gins¹⁷⁹ performs

¹⁷⁴ REGAN, J. C. Arch. Pediat. 61: 63, 1944

¹⁷⁵ COHEN, R. Kentucky M. J. 38: 40, 1940

¹⁷⁶ DAVIDSON, L. S. P., and DAVIS, L. J. Lancet 2: 103, 1943

¹⁷⁷ TIÈCHE, M. Schweiz. med. Wchschr. 53: 448, 1923

¹⁷⁸ GINS, H. A. Ztschr. f. Hyg. u. Infektionskr. 106: 213, 1926

¹⁷⁹ HOOKER, S. B. J. Infect. Dis. 45: 255, 1929

the test on vaccine immune guinea pigs instead of human beings

9 INFLUENZA

Beveridge and Burnet¹⁷⁴⁰ studied the effects of intradermal injection of influenza virus antigens in normal subjects. They found that intradermal inoculation of a 1:10 dilution of unheated or boiled allantoic fluid infected with influenza virus A or B produced a cutaneous reaction in most adults and in some children. Partial purification of the virus did not reduce its capacity to cause reactions. No response was obtained with normal allantoic fluid or with suspensions of chick tissue containing several times as much protein. While in adults the size of the reaction could not be correlated to the serum antibody titer, almost all the children reacting positively were shown by serologic test to have been infected in the past by the corresponding viruses. The authors suggest that allergy to the virus may play a part in resistance to influenzal infection and when infection does occur in the production of symptoms.

Dingle and Seidman¹⁷⁴¹ found that a specific carbohydrate isolated from the type B influenza bacillus could be used for skin testing in the same way as pneumococcus polysaccharide. Its clinical applicability has not yet been determined.

10 MUMPS

A skin test indicative of previous infection with the virus of mumps was developed by Enders¹⁷⁴² using as antigen a heat inactivated suspension of the parotid gland of a monkey infected with the virus. Failure to react signified in most instances potential susceptibility while of several hundred subjects with positive reactions only a very few subsequently developed the disease. The results of the test also corresponded with observed fluctuations in the specific complement fixing antibodies in man and monkey during and after infections with the mumps virus. In a series of human subjects antibodies occurred in about 92 per cent of the serums of those giving

a positive history of mumps but in only 50 per cent of those who denied having had the disease. Subsequent study indicated that an inapparent infection produces the same degree of immunity as an overt attack. The Enders test may be of particular value in the diagnosis of cases of *encephalitis without definite parotitis* but suspected nevertheless of being due to infection with the virus of mumps. Recently the virus has been grown on the yolk sac of the chick embryo and has been reported to give reliable dermal reactions in immune persons (Habel¹⁷⁴³) if this is confirmed a ready source of antigen for skin testing will be available.

11 ANTHRAX

The relationship of the skin to anthrax infection was long a controversial question. Besredka¹⁷⁴⁴ had claimed that guinea pigs could not be infected by anthrax bacilli unless the latter were given an opportunity to adhere to the skin. But this claim has been refuted by many investigations (Busson, Sobernheim, and others) showing that animals can be infected by intracerebral inoculation (contact with the skin during the injection being carefully avoided) as well as by mouth. Furthermore, Besredka's assumption that immunity to anthrax can be achieved only by way of the skin and without the aid of specific humoral antibodies has recently been categorically rejected. For the fact that humoral antibodies cannot be demonstrated is not accepted as conclusive evidence since it is well known that these antibodies are not responsible for the changed allergic reactivity and for the immunity of the tissues. The view that antibodies play a definite role in anthrax will receive additional support if Zironi's findings can be confirmed; this author reported that the reactivity of the skin of normal animals can be altered by serums containing specific antibodies and also that injection of killed anthrax bacilli evokes a delayed inflammatory reaction in the skin of previously infected animals.

12 UNDULANT FEVER (BRUCELLOSIS)

The two types of undulant fever, or brucellosis, were formerly regarded as two distinct

¹ BEVERIDGE W. I. B. and BURNET F. M. M. J. Austral. J. 85 1944

DINGLE J. H. and SEIDMAN L. R. Proc. Soc. Exper. Biol. & Med. 46 31 1941

² ENDERS J. F. Ann. Int. Med. 18 1015 1943

³ HABEL K. Pub. Heal. & Rep. 60 201 1945

entities: (1) Malta fever, caused by *Brucella melitensis*; and (2) Bang's disease, caused by *Br. abortus*. The last-named is responsible for the infectious abortion disease of cows and hogs. Both diseases can be transmitted to man, particularly through drinking contaminated cow or goat's milk.

The clinical types and the serologic and skin test reactions would seem to indicate that Malta fever and Bang's disease are caused by closely related if not identical organisms.

These infections bring about an alteration in the capacity of the skin to react to brucellergin—a term now applied to both melitin and abortin, nucleoprotein substances derived from *Br. melitensis* and *Br. abortus*, respectively. The reaction is generally of the delayed-inflammatory type. Urschel¹⁷⁴ compared the different antigens in routine skin testing for brucellosis, including brucellergin, and heat-killed suspensions of *Br. abortus*, of *Br. suis*, and of both combined. He, as well as others, found that the vaccines often caused local necrosis and were more likely to produce systemic reactions, so that brucellergin is the antigen of choice. According to Griggs,¹⁷⁵ the initial dose for skin testing should be 0.1 cc of a 1:120,000 dilution or less. The brucellergin test is held by some authorities to be far more reliable diagnostically than the agglutination method, a negative reaction ruling out the disease except in a small percentage of cases of chronic brucellosis, while a positive reaction almost always denotes previous or present contact with *Brucella* organisms, though not necessarily overt disease.

While the test appears to be specific, its value is depreciated by the following facts. The sensitiveness to brucellergin may not develop until late in the course of the disease. The reaction will continue to be positive long after the disease is cured, as well as in persons who were exposed to contact but did not present any clinical manifestations, particularly veterinarians, milkers, and laboratory workers. Thus, Huddleson¹⁷⁶ observed a direct relationship between positive reactions to *Brucella* antigen in symptom-free individuals and their opportunity for exposure to infected

animals or substances. The sensitivity increases on repeated contacts. Huddleson predicts that 90 per cent of veterinarians treating brucellosis in animals will become sensitive within a period of two years. Occasionally nonspecific reactions occur in other diseases, such as tuberculosis, apparently on a metallergic basis. Therefore, the skin test is of value only when considered in connection with the clinical and serologic evidence. It should also be kept in mind that the intradermal test may stimulate a marked rise in agglutination or opsonocytophagic titer even in normal subjects. Hence the latter tests should be performed before skin testing.

Certain symptoms suggest the presence of local hypersensitiveness to *Br. abortus*. They include the skin manifestations, described by Huddleson and Johnson,¹⁷⁷ Haxthausen and Thomsen,¹⁷⁸ and others, that develop on the forearms after manual delivery of cows infected with Bang's bacilli. Two types of lesions are observed. The first type consists of erythemas that develop very rapidly and disappear within a few hours. In these cases Huddleson and Johnson observed immediate-urticarial skin reactions to abortin antigen. W. Jadassohn,¹⁷⁹ however, suggested that these erythemas may be attributable to hypersensitiveness to cow protein, because they are practically identical with the skin manifestations experimentally produced with beef broth. The second and far commoner form consists of papular, intensely itching eruptions that develop after a number of hours and persist for from several days to three weeks. In these cases there is a delayed-inflammatory reaction to abortin. Both types show a pronounced tendency to recur whenever the skin comes into contact with Bang's bacilli. Inunction of abortin into the skin of patients results in a local exanthem similar to the second form described above.

Both these reactions are apparently the expression of a local allergy. In addition, there are a few reports suggesting the possibility of a generalized allergic process. Makkawejsky and Karkadinowsky described bullous-hemorrhagic dermatides appearing on the forearms

¹⁷⁴ URSCHEL, D. L.: Indiana State M. J. 38, 5, 1935.

¹⁷⁵ GRIGGS, J. F.: Ibid. 37: 241, 1934.

¹⁷⁶ HUDDLESON, I. F.: J. S. C. Vet. 4, 10, 1913-44.

¹⁷⁷ IDEM, and JOHNSON, H. W.: J. A. M. A. 94: 1905, 1930.

¹⁷⁸ HAXTHAUSEN, H., and THOMSEN, A.: Arch. f. Dermat. u. Syph. 163 477, 1931.

several days after the patients had removed infected placentae. These skin manifestations then spread to other parts of the body accompanied by unbearable pruritus, malaise, chills, and fever, and sometimes also by gastro-intestinal disturbances, severe rheumatoid pains, and swelling of the joints.

The senior author¹⁷⁴³ observed two additional generalized allergic forms: one suggested an erythema multiforme exudativum and was characterized by hemorrhagic bullae and generalized pains in the joints; the second presented a clinical picture similar to that of dermatitis herpetiformis (Duhring). In both conditions there was a strongly positive cutaneous reaction associated with focal and general manifestations. Specific antibodies were demonstrable by means of Mueller's agglutination method.

In treating 100 cases of chronic brucellosis with various brucella vaccines and filtrates, Griggs¹⁷⁴⁵ found some of such extreme hypersensitiveness that they could not tolerate a dose of even a fraction of 1 brucella bacterium. By serially diluting the vaccine, it was found that some of them could be given doses of oxidized vaccine equivalent to the amount of specific substance theoretically present in 0.00002 of 1 bacterium. The senior author observed a similar extreme hypersensitiveness in a veterinarian who manifested very marked local and systemic reactions to the injection of 1 bacterium. Such quantities are not as ridiculously small as they appear since according to the theories of physical chemistry the size of the protein molecule is such that specific proteins are present in doses as small as 1×10^{-14} of a bacterium. Griggs observed that by the use of sufficiently minute doses, desensitization and immunization performed alternately and repeatedly in the same case gave encouraging results. Others have reported encouraging therapeutic results with brucellergen.

13 CHANCROID (ULCUS MOLLE)

By means of intracutaneous reactions to Ducrey's bacillus vaccine, it is possible to demonstrate that the reactivity of the skin of ulcer molle patients has been specifically altered, particularly so when the course of the

disease is complicated by chancroidal bubos (Ito¹⁷⁵⁰). For this test, Reenstierna⁷⁵¹ employed a suspension of bacilli that had been killed by two weeks on ice. The reaction is of the delayed inflammatory type. However, it must be remembered that the positive skin reaction is not obtained until about the twentieth day of the disease; different reports vary from six days to five weeks. It is important to note that the altered reactivity of the skin persists for decades after the disease has been cured, and possibly for a lifetime. Thus, in one survey, one third of a series of Negro adults not known to have had chancroid recently gave positive reactions (Heyman et al.¹⁷⁵²). Within the limits of these reservations, the test is generally considered highly diagnostic. However, more recent studies indicate that only 70 to 80 per cent of proved cases exhibit positive skin tests, and that those with negative reactions are likely to remain so on retesting some weeks later (Heyman et al.¹⁷⁵²).

To its successful passive transfer experiments with animal serum, and the demonstration of complement-fixing antibodies in the blood of chancroid patients, seem to indicate that antibodies play a role in the development of the positive intracutaneous reaction. Furthermore, the good results obtained with vaccine therapy (e.g., Dmelcos vaccines) and the local, focal, and general reactions appearing in the course of this treatment point to an alteration in the reactivity of the organism.

14 GONORRHEA

The great majority of the authors who have investigated the cutaneous and intracutaneous reactions to living or killed cultures of gonococci have come to the conclusion that skin tests are of no practical diagnostic value in this condition, since numerous healthy control subjects gave positive reactions (for bibliography, see Pooman¹⁷⁵³).

Engel, on the other hand, claims to have achieved specific reactions with the soluble gonotoxin complex and that its specificity was confirmed by successful passive transfer

* ITO T. *Arch. f. Dermat. u. Syph.* 116: 341, 1913.

REENSTIERNA J. *Acta dermat. ven. col.* 2: 1, 1921.

HEYMAN A., BEESON P. B. and SHELDON W. H. *J. A. M. A.*

129: 935, 1945.

1750 POOMAN A. *Zentralbl. f. Haut u. Geschlecht k.* 50: 1, 1935.

of the hypersensitiveness by the Prausnitz-Kuestner technic. However, the significance of these toxin reactions has also been hotly disputed.

Other authors (Casper; Dmitriew and Demidowa) are of the opinion that they have discovered a diagnostically useful specific antigen in the polysaccharide fraction of the gonococcus. Corbus and his associates¹⁷³⁴ recommend the bouillon filtrate for eliciting a sharp cutaneous response. This recommendation was seconded by Conrad and Wishengrad.

Although it has not yet been conclusively proved that there is an allergic reactivity of the skin in gonorrhea, the existence of an immunobiologic process is strongly suggested by a number of observations: for example, by the presence of complement-fixing antibodies.

D. CHRONIC INFECTIOUS DISEASES

1. TUBERCULOSIS

Ever since the publication of Koch's fundamental experiment (1891), it has been known that a tuberculous organism reacts differently to reinfection than to the initial infection, and that this altered reactivity is generally expressed by manifestations of increased local sensitiveness. Thus, a healthy animal responds to infection with tubercle bacilli by the formation, after about two to fourteen days, of a hard nodule at the site of infection, which develops into an ulcerous lesion, until the animal finally succumbs to the infection. On the other hand, tuberculous guinea pigs respond to the administration of tubercle bacilli with edema, hemorrhage, and necrosis in the site of injection within from one to two days—manifestations that soon retrogress, however, without having been accompanied by any appreciable systemic involvement (see Table 2).

The questions of the relationship and interdependence of allergy and immunity in tuberculosis have been discussed in some detail in chapter II. Here we shall consider primarily the extent to which immunobiologic, anatomic, and clinical phenomena are interrelated in tuberculosis.

Ranke¹⁷³⁵ identified the following three immunobiologic states in tuberculosis: the primary complex, the generalized forms, and chronic isolated organ tuberculosis. In the first stage, the so-called primary lesion develops at the site of infection, in association with enlargement of the regional lymph glands (primary complex). In the overwhelming majority of all cases, the primary complex is to be found in the lungs; second in order of frequency, in the gastrointestinal tract; and in only a small percentage in the other organs, including the skin. Allergy subsequently develops after a certain incubation period, the length of which is determined primarily by the type of infection: because of the very rapid dissemination of the bacilli, the incubation period in intracardiac infections in animal experiments is much briefer—taking about ten days—than it is after subcutaneous or intracutaneous infections, in which from two to six weeks are required. In human beings, the allergic state commences about eight weeks after the infection (E. Loewenstein). At this time the tuberculin reaction becomes positive.

When the disease progresses beyond the primary complex, it enters into the second stage, in which the bacilli are distributed throughout the organism by way of the blood and lymph vessels, thus bringing on generalized tuberculosis. This stage is characterized by a marked degree of hypersensitiveness, manifested by unusually strong reactions to tuberculin.

Just as the disease may fail to progress beyond the phase of the primary complex, so too it may come to an end during the second stage. But when it continues to progress, it enters into the third stage, in which the hypersensitiveness becomes less and less evident and is, in fact, replaced by a certain degree of hyposensitiveness or even immunity, this usually suffices to prevent further hematogenous or lymphogenous metastases. The disease is thus confined to the organs already affected, enters upon a long course, with a tendency to spontaneous involution (e.g., chronic lupus). But even in this case, the condition can progress by contiguity—for example, by extension from a tuberculous lymph

¹⁷³⁴ CORBUS, B. C., and CORBUS, B. C., *J. A. M. A.* 116: 113, 1941.

¹⁷³⁵ RANKE, K. E. *Ausgewählte Schriften zur Tuberkulosepathologie*. Berlin, 1923.

gland to the skin. The tuberculin reaction is now manifested by only slight local focal and general responses since the organism has acquired a high degree of tolerance to tuberculin. This state can ultimately develop into one of positive anergy.

It must not be denied however that Ranke's¹⁷⁵⁵ pattern does not always strictly coincide with clinical observations. One rarely encounters at autopsy perfectly clear cut examples of the first second or third stage what is usually observed is a combination of exudation and proliferation. Quite commonly evidence of various types of allergy are observed in one patient and even in one organ. According to Pagel¹⁷⁵⁶ each focus of infection passes through the various allergic stages. It is therefore not the presence of a single form of allergic tissue reaction but the predominance of one and the rate of transition from one form to another that is characteristic of the pathologic anatomic picture of the tuberculous process (Staehehn¹⁷⁵⁷). It should be borne in mind that tuberculous allergy does not in the course of time change more or less abruptly from one type to another but that the hypersensitiveness expressed by acute tissue reactions slowly and gradually passes over into a state of relative insensitiveness characterized by chronic proliferative tissue reactions. And it must be remembered furthermore that this change does not occur simultaneously throughout the organism rather the transition takes place at different times in the different organs. However despite a number of modifications to which it has been subjected in the course of time the basic principle of Ranke's¹⁷⁵⁵ doctrine is still valid—namely that the course of a tuberculous disease is dependent to a considerable extent upon the organism's hypersensitiveness.

The diversity of the manifestations of tuberculosis may be explained on the basis of the variations in the influence exerted by the three following factors: the individual's predisposition, the number and virulence of the bacilli and the immunologic state of the organism. As specifically regards the his-

tologic aspects of tuberculous allergic hypersensitiveness the following forms are differentiated: (1) the progressive caseous type which occurs when there is excess tuberculous antigen and only a small supply of antibodies; (2) the exudative form caused by the presence of much tuberculous antigen and high antibody content; (3) the proliferative type resulting from the reaction between a relatively small amount of antigen and a large supply of antibodies.

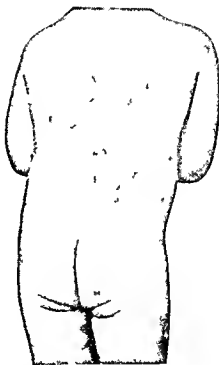


FIG. 226. LICHENOID FORM OF TUBERCULID (LICHEN SCROFULOSORUM)

Tuberculosis of the skin has been subdivided by J. Jadassohn⁴ according to the type of allergic tissue reaction into three groups: (1) the so-called classic tuberculosis; (2) the tuberculids; (3) the positive anergic forms. The first group comprises tuberculosis luposa (lupus vulgaris) showing typical tuberculous structure and few bacilli, as well as tuberculosis verrucosa cutis, tuberculosis colliquativa (scrofuloderma) and tuberculosis ulcerosa miliaris. All these forms are distinguished by a particularly high degree of tuberculin hypersensitiveness. The tuberculids may be divided into the lichenoid (Fig. 226) papulo-

⁴ PAGEL, W. In: Kayne, G. G., Pagel, W. and O. Shaughnessy. Pulmonary Tuberculosis. New York: Oxford, 1939.

¹ STAEHEHN, R. Helvet. med. acta 1: 568, 1933.

necrotic (Fig. 227), and indurative forms. Bacilli are hardly ever found here, either microscopically or by means of cultures, histologically, there is a combined picture of

and Darier-Roussy's sarcoids, lupus pernio, and lupus miliaris (Kaposi). Most of these forms have thus far been found to be free of bacilli and are characterized, in addition, by a tissue rich in epithelioid cells, as well as by the absence of inflammation. This entire group is marked by the almost invariable absence of cutaneous hypersensitiveness to tuberculin (specific positive anergy). It is noteworthy, furthermore, that when cutaneous tuberculosis (especially lupus vulgaris) is complicated by visceral tuberculosis, there is a tendency toward lessened sensitiveness to tuberculin, while if active visceral and cutaneous tuberculosis coexist, the tendency is toward increased sensitiveness (Bonnevie and With^{17,18}).

Volk's^{19,20} classification presents a clear and concise picture (Table 39)

TUBERCULIN

Today there seems to be little if any doubt as to the allergic character of numerous clinical manifestations of tuberculosis in human beings and animals. Until quite recently, however, the question as to whether only the tubercle bacillus, or Koch's old tuberculin as well, could be considered as the antigen, was still bitterly controversial. The positive tuberculin reaction in tuberculous human beings and animals unquestionably corresponds to the early reaction noted in Koch's fundamental experiment. However, the facts that in

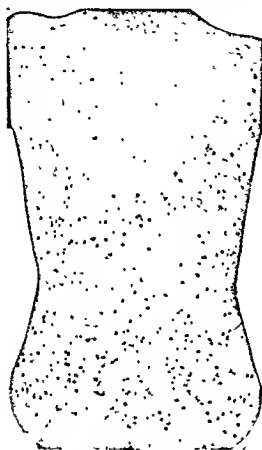


FIG. 227. PAPULONECROTIC TUBERCULID

TABLE 39—Relation of Cutaneous Tuberculosis to Degree of Infection and State of Immunity

Site of Infection	Abundant Tubercle Bacilli Absent or Scant Antibody Content	Moderately Numerous Tubercle Bacilli Scant to Moderate Antibody Content	Numerous Tubercle Bacilli High Antibody Content
Cutis	disseminated military tuberculosis	hematogenous lupus (lupus miliaris faciei, postexanthematous lupus)	tuberculids (tuberculosis lichenoides, papulonecrotic tuberculid)
Subcutis	multiple tuberculous abscesses	tuberculous gummata (colligative tuberculosis)	indurative tuberculosis (erythema induratum of Bazin)

tubercles and banal inflammation. As a rule, rather strong doses of tuberculin are required to produce a positive cutaneous reaction in patients with tuberculids. The more or less anergic forms of tuberculosis include Boeck's

human beings it is generally impossible to achieve allergization with tuberculin, and that

^{17,18} BONNEVIE, P., and WITTS, T. K. Arch f Dermat u Syph 175 181, 1937

^{19,20} VOLK, R. Tuberkulose der Haut. In Handb der Haut u Geschlechtskr., vol 19, pt 1, 1931

the tuberculin test is invariably negative in passively immunized animals as well as in noninfected offspring of a tuberculous mother animal, have been advanced by a number of authors as arguments against the antigenicity of tuberculin. Nevertheless, in recent years, more and more authorities have come to accept the view—although they have to resort to various working hypotheses—that there is such a thing as a genuine allergy to tuberculin, that, indeed, such an allergy must exist in order to permit a logical explanation of the fact that the tuberculin test demonstrates the specific hypersensitiveness of an individual infected with tuberculosis.

Thus, Moro and Keller and other authors succeeded, by the local injection of conjugate protein antigens (tuberculin plus cowpox lymph or organ extracts from normal animals), in producing hypersensitiveness to tuberculin in nontuberculous infants, furthermore, they similarly achieved allergy to tuberculin in animals without resorting to tuberculous infections. Fernbach and Siegel, however, dispute the specificity of the hypersensitiveness produced in this manner.

As to the passive transfer of tuberculin hypersensitiveness by means of animal experimental methods or the Prausnitz Kuestner procedure, while the literature contains reports of numerous negative results, there are some unequivocally positive ones (Bruck, Lehner and Rajka, Biberstein and Giesser, Konrad¹⁷⁶⁰, Corper and Cohen¹⁷⁶¹, and others). The latter, of course, were encountered only in cases with an extraordinarily high degree of cutaneous tuberculin allergy. Chase⁶⁶⁸ found that cellular passive transfer was possible in guinea pigs which had been rendered hypersensitive to tuberculin by subcutaneous injection of killed tubercle bacilli suspended in liquid petrolatum. After five to nine weeks when cutaneous reactivity to tuberculin was pronounced, exudates were induced in the peritoneal cavities by intraperitoneal injections of liquid petrolatum, and consisted mainly of large mononuclear cells. These cells, after washing, were injected into normal guinea pigs, which manifested tuberculin hy-

persensitiveness after two or three days following intraperitoneal injections or twenty to thirty six hours following intravenous injection. Similar transfer was never effected with the donor's serum or with the peritoneal exudates of nontuberculous guinea pigs.

In this connection certain substances must be mentioned—the so called procutines which Fellner demonstrated in tuberculin papules, and which have the property of enhancing the effect of tuberculin. These findings have been confirmed by the extensive investigations of Martenstein and Schapiro Hoke and Lang, and Wichmann. Moreover, it has also been possible to demonstrate the presence in tuberculin papules of substances—the so called anticutines—that inhibit the tuberculin effect (Pickert and Loewenstein Jadassohn and Martenstein¹⁷⁶²). These have been detected particularly in patients with skin manifestations associated with positive tuberculin allergy. Since it has been ascertained that the tuberculin inhibiting substances are as a rule thermolabile and that the enhancing substances are not, it is now possible to separate them. In addition to these tuberculin inhibiting and tuberculin enhancing substances, the serum of tuberculous patients has been found to contain certain complement deviating precipitating, and agglutinating antibodies. Moreover, Corper and Cohen¹⁷⁶¹ showed that the blood from tuberculin immune guinea pigs prevented tuberculo-protein sensitization and tuberculin anaphylactic shock when injected into normal guinea pigs, but not in those already tuberculin sensitive. The bulk of this evidence makes it appear more than likely that the tuberculous organism's altered reactivity to tubercle bacilli and their products is attributable to the action of antibodies.

The following points are also worthy of note.

(1) The very commonly observed increase in the degree of tuberculin hypersensitiveness in a tuberculous individual resulting from repeated injections of tuberculin is followed in time by a decrease in the hypersensitiveness. While the phenomena of sensitization and desensitization do not, in themselves, con-

¹⁷⁶⁰ KONRAD J. Wien klin Wchnschr 45 1084 1108 1134 1932

¹⁷⁶¹ CORPER H. J. and COHEN M. L. Am Rev Tuberc 48 329 1943

¹⁷⁶² JADASSOHN, W. and MARTENSTEIN H. Klin Wchnschr 2 1210 1923

clusively prove that antibodies take part in the given reaction, analogy with other allergic states at least strongly suggests such a mechanism.

(2) The assumption that antibodies are involved is supported by the fact that tuberculous foci and the sites of former tuberculin reactions flare up after injections of tuberculin—observations that surely could be most readily explained by the presence of antibodies.

(3) A similar mechanism is suggested by the occasionally encountered iris-like or corymbiform tuberculin reactions, because analogous reactions are observed in serum sickness and in other conditions in which the action of antibodies is generally accepted.

(4) The appearance of tuberculin exanthems may also be regarded as the expression of an antigen-antibody reaction. These cutaneous manifestations, which take the form of urticarial, lichenoid, and occasionally even bullous eruptions, sometimes appear after unusually strong local responses to the intracutaneous administration of tuberculin, Pirquet tests (Kristjansen), or even Moro tests (Geissler). This group in all probability should also take in the so-called early tuberculous exanthems that can be erythema-multiforme-like (Uffenheimer, von Moritz). The early exanthem is most commonly observed in the transitional stage between the preallergic and the allergic phases, when the tuberculin reaction is still negative—in other words, at the end of the primary and at the beginning of the secondary stage. The significance of the manifestation lies in the fact that diagnostically it is equivalent to a positive tuberculin reaction.

An unusual case of tuberculin exanthem, which was described in detail by Konrad¹⁷⁶⁹ and in which the senior writer succeeded in passively transferring the tuberculin hypersensitiveness, seems worthy of special mention here, and is illustrated by the two accompanying photographs (Figs. 228, 229).

(5) Employing a preparation of purified principle of old tuberculin—the so-called β -tuberculin—Kallós¹⁰⁹ succeeded in evoking immediate-urticarial skin reactions as well as specific uterine contractions (Schultz-Dale technic) in tuberculous guinea pigs. He concluded, therefore, that the reaction to tuberculin is to be regarded as an allergic



FIG 228 UNUSUAL CASE OF TUBERCULIN HYPERSENSITIVENESS

Papulovesicular exanthem appeared after intracutaneous tuberculin test that produced necrotic reaction (Fig 229)



FIG 229 HYPERERGIC REACTIONS TO OLD TUBERCULIN
Upper, to 1:100,000 dilution, lower, to 1:1,000,000 dilution Same patient as in Fig 228

phenomenon based on an antigen-antibody reaction. Similar experiments had previously

been reported by W. Jadassohn. Likewise Chase¹⁷⁶³ was able passively to transfer tuberculin sensitivity with the serum of guinea pigs which had been immunized simultaneously with killed tubercle bacilli in paraffin oil and with a conjugated antigen. Lastly Seibert,¹⁷⁶⁴ employing purified tuberculin protein, succeeded in establishing in animals a high degree of allergy, which could be transferred passively. The antibody to tuberculin protein (P.P.D.) can be demonstrated by means of the precipitin test, electrophoretic identification, and uterine strip contraction (Seibert¹⁷⁶⁵).

From this discussion, it will be seen that the question whether tuberculin is to be regarded as an antigen can today be answered in the affirmative almost with experimental certainty. Moreover, on the basis of their original work, Lewis and Seibert¹⁷⁶⁶ concluded that the antigenicity of tuberculo-protein can be favorably compared with that of other well known protein antigens such as egg albumin and horse serum. Thus, Corper and Cohen¹ showed that guinea pigs could be anaphylactically sensitized to tuberculo-protein; that the sensitivity could be passively transferred in many instances, and that desensitization could be accomplished by appropriate treatment.

On the other hand, Seibert¹⁷⁶⁷ has demonstrated that the purified protein derivative of tuberculin (P.P.D.) is in itself incapable of producing antibodies but can elicit a skin reaction in a tuberculous organism; furthermore, P.P.D. can be rendered antigenic by adsorbing it on aluminum hydroxide, thus demonstrating its hapten nature. It is prepared by growing the tubercle bacillus on a synthetic protein free culture medium, thus avoiding contamination with foreign protein. This refined tuberculo-protein has largely replaced the highly complex and variable old tuberculin for diagnostic purposes. The first dose of P.P.D. is 0.00002 mg., which is equivalent to from 0.002 to 0.01 mg. of Koch's old tuberculin (the strength of the latter varies with different preparations), the second dose of 0.005 mg. is approximately equivalent to 1

mg. of old tuberculin. In cases of manifest tuberculosis it is advisable however to test with one tenth or one hundredth of the first dose in order to prevent too strong a reaction. In the undiluted dry form tuberculin P.P.D. is stable practically indefinitely. Once diluted it maintains its potency for a few days at refrigerator temperatures.

Because of its standard potency, stability, simplicity of preparation and freedom from extraneous proteins, the purified protein derivative of Seibert is considered by the National Tuberculosis Association as superior to old tuberculin. Many authors have compared the two tuberculins as to accuracy, and have found a remarkable conformity. In this connection the work of Thomas¹⁷⁶⁸ on patients with tuberculous dermatoses is particularly worthy of note.

Let us now briefly consider the clinical value and the practical significance of the tuberculin tests.

The specificity of the tuberculin reaction with Koch's old tuberculin* is now almost universally recognized. However, according to Zieler and Haemel a reaction is to be interpreted as positive only when its maximum is attained after forty eight hours or when it persists for at least that long and when it retrogresses gradually. Furcolow et al.¹⁷⁶⁹ hold that cutaneous reactions elicited only with large doses are probably non specific, and suggest that the test dose of tuberculin should not exceed 0.0001 mg. Subsequent subcutaneous injection of old tuberculin will cause the test site to flare up and to present what can be histologically identified as a tubercloid structure.

As to the diagnostic value of the tuberculin test, it may definitely be said that a positive reaction in infants clearly proves the presence of a positive tuberculous process, and that a negative result in older children is generally an indication of the absence of tuberculosis—thus the absence of a reaction can be of decisive differential diagnostic significance in

* Old tuberculin is a filtrate of broth cultured tubercle bacilli killed by live steam, concentrated to one tenth of its original volume.

¹⁷⁶³ THOMAS C. C. Arch. Dermat. & Syph. 45: 544, 1942.

¹⁷⁶⁹ FURCLOW M. L., HEWELL B., NELSON W. E. and PALMER C. B. Pub. Health Rep. 56: 1282, 1941.

¹⁷⁶³ CHASE M. W. Proc. Soc. Exper. Biol. & Med. 52: 238, 1943.

¹⁷⁶⁴ SEIBERT F. B. ibid. 30: 1274, 1933.

¹⁷⁶⁵ Idem and NELSON J. W. ibid. 49: 77, 1942.

¹⁷⁶⁶ LEWIS J. H. and SEIBERT F. B. J. Immunol. 20: 201, 1931.

¹⁷⁶⁷ SEIBERT F. B. Am. Rev. Tuberc. 30: 713, 1934.

cases of doubtful lung affections or of puzzling joint or bone diseases.

The extensive studies of de Assis¹⁷⁷⁰ prove that during the course of the tuberculous primary infection of infancy, the tuberculin allergy of the skin is established progressively through a preallergic period ("infratuberculin allergy") the presence of which has not been previously demonstrated. The intradermal inoculation of dead bodies of the tubercle bacillus (0.1 mg. of BCG vaccine killed by heat) in children who are in the preallergic period is accompanied by specific and characteristic reactions that permit the recognition of the preexistence of a virulent tuberculous infection before the appearance of cutaneous allergy and consequently of the X-ray signs and the local and general clinical symptoms. These reactions are characterized by a rapid and intense nodular infiltration at the site of inoculation at least 5 mm in diameter and presenting in some instances, even at this early stage, caseation. No definite relationship could be established between these local changes and the early causes of tuberculin hypersensitiveness. Oral revaccination with living BCG did not exert any apparent influence on the frequency or intensity of the latent allergy.

In adults, according to numerous authors, only a negative test is of any significance: the absence of reaction implies freedom from tuberculosis—provided that the test made with 1 mg. intracutaneously is negative, and that there are no clinical conditions present that might make for a negative anergy. For it must be remembered that positive tuberculin reactions fail to appear, for a while, in the presence of certain infectious diseases (measles, varicella, whooping cough, and grippe), of fever, in the early stages of pleural and peritoneal effusion, and occasionally also during the menstrual period and pregnancy, as well as throughout the course of miliary tuberculosis, tuberculous meningitis, and tuberculous cachexia (see p. 24). On the other hand, a positive tuberculin test in an adult indicates nothing more than that the individual has, at some time or other, had a tuberculous infection; and that the altered reactivity resulting

from the interaction between the bacilli and the organism still persists. Lastly, it should be noted that the tuberculin reaction may be increased by repeated injections of tuberculin, as well as by repeated administration of other bacterial protein (e g., in the form of vaccines). However, Levine and Sackett¹⁷⁷¹ and Furcolow et al.¹⁷⁶⁹ deny that frequent inoculations with tuberculin are capable of inducing cutaneous sensitivity, even in large doses (100 mg.), nor did they find any evidence that local sensitization of the tissues results from repeated tuberculin tests in the same dermal area.

It is still a highly controversial question whether or not the strength of a tuberculin reaction is to be considered as a definite measure of the individual's degree of immunity. Relatively few observations support the view that there is a certain relationship between the activity of the tuberculosis and the intensity of the tuberculin reaction. Thus, Cummins, in a study of mine workers in South Africa, found that 15 per cent of the individuals giving strongly positive reactions eventually acquired the disease, of those giving weak reactions, only 7 per cent, and of those not reacting at all, only 3 per cent were subsequently found to have symptoms of active tuberculosis. Equally undecided is whether a tuberculin-positive or a tuberculin-negative individual is more likely to develop active tuberculosis. Kane¹⁶⁵⁴ cites an approximately equal number of reports indicating (1) that a positive test is a definite index of relative immunity, (2) that the incidence of the development of tuberculosis is higher in tuberculin-positive groups than in tuberculin-negative groups, and (3) that there is no difference in the incidence of pulmonary tuberculosis between negative and positive reactors.

It has been claimed by various authorities that the hypersensitiveness to tuberculin gradually regresses in cases in which the tuberculosis is really cured. Not infrequently, calcified pulmonary lesions are demonstrable on the roentgenograms of persons who are tuberculin negative. Moreover, large series of subjects followed by repeated tuberculin tests show a reversal of the reaction from positive to negative in a certain proportion of cases (2 to 11

¹⁷⁷⁰ DE ASSIS, A.: Foreign Letters, J. A. M. A. 173: 615, 1943, 124, 242, 1944.

¹⁷⁷¹ LEVINE, M. L., and SACKETT, M. F.: Am. J. Dis. Child. 44: 1014, 1942.

per cent, according to various investigators) over a period of years. On the other hand, very strong tuberculin reactions are occasionally observed in individuals who have no history of active tuberculosis and who further, do not later develop this disease.

On the basis of extensive experimental investigation Appel and his associates¹⁷⁷ recently arrived at the conclusion that there is no such thing as a constant relationship between the activity of the disease and the intensity of the tuberculin reaction. Therefore, the tuberculin reaction is to be interpreted as only an index of susceptibility rather than as an indication of infection (Corper). On the other hand, in a necropsy study of 29 cases, Brosius and Woodruff¹⁷⁸ found some correlation between tuberculin anergy and the number of acid fast bacilli in the lesions. Thus, in cases with little or no tuberculin sensitivity, many bacilli were present and appeared to be proliferating. In those with marked reactivity before death, few or no bacilli were found, and then only in caseous tissues or exudates. This is explained by the avascular barrier of the cavities, which prevents the passage of the immunity or growth inhibiting factors present in the sensitized tissue from reaching and destroying the bacilli by lysis.

The strong tuberculin reactions encountered in cases of rheumatoid arthritis are also striking. Such responses are not to be interpreted, however, as proof of the tuberculous character of all these cases, but rather as a metallergic reaction. This means that there is not only a specific hypersensitiveness to the bacteria responsible for the rheumatic condition, but also a metaspecific reactivity to tuberculin. Nor are the strongly positive tuberculin reactions often observed in asthmatic patients to be considered as specific. Although it is generally true that in certain forms of tuberculosis the reactions to tuberculin are especially strongly positive it must be remembered that exceptions to this rule are by no means uncommon, it is imprudent, therefore, to assume that a strongly positive reaction in an adult is necessarily proof that a given disease (e.g., an arthritic disorder) is due to tuberculosis.

The result of a single tuberculin test is of little if any value in determining the degree of activity of the disease process or in aiding the physician to venture a prognosis. Attempts have been made to draw conclusions from the relative intensity of the reaction following a second injection of tuberculin. A stronger reaction following the second injection was supposed to favor the diagnosis of an active tuberculous process. But Reichel and Milbradt found that this increased response was given by no less than 60 per cent of the clinically healthy individuals tested.

Four different tuberculin skin tests are available at present:

(1) The cutaneous tuberculin test or Pirquet test (for technic, see p. 159). If this test proves negative, an intracutaneous test should be performed forty eight hours later. The interval should be no longer, since cutaneous allergization of the tuberculous organism sets in after four days. A positive cutaneous reaction to undiluted old tuberculin is of about the same intensity as the reaction to an intracutaneous injection of a 1:10,000 dilution (0.01 mg.). The chief disadvantage of the Pirquet method of administering tuberculin is that there is no way of knowing how much tuberculin actually enters the organism from the abraded area.

(2) The intracutaneous method of Mantoux¹⁷⁹ (for technic, see p. 161).

(3) The percutaneous method of Moro, which consists of inoculation into the skin of a 50 per cent tuberculin ointment composed of equal parts of hydrous wool fat and pure tuberculin (Fig. 54 p. 172).

(4) The patch test method* with tuberculin, first conceived by Lautner (1908), rediscovered by Nathan and Kallos^{179a} and perfected by Vollmer and Goldberger^{179b}. The tuberculin patch test is simple, practical and reliable (Figs. 230-231). It is somewhat more sensitive than the Pirquet test and slightly less sensitive than the Mantoux with 0.1 mg. of old tuberculin. For routine work, the Vollmer

* It is of interest to note that the patch test method has been used with trachophytin by Salzsberger and Lewis¹⁸⁰ and with ovalomycin by Rameel and Benzger¹⁸¹.

¹⁷⁷ Appel, J. M., Douglas, B. H., Jocz, T. R. and Willis, H. S. *Am. Rev. Tuberc.* 36: 303, 1937.

¹⁷⁸ Brosius, W. L. and Woodruff, C. E. *Ibid.* 50: 473, 1944.

¹⁷⁹ Nathan, E. and Kallos, P. *Klin. Wchnschr.* 10: 2392, 1931.

^{179a} Vollmer, H. and Goldberger, E. W. *Am. J. Dis. Child.* 43: 1019, 1937.

patch test can be recommended as the initial test in place of that of Pirquet. If it is negative at the end of one week, a Mantoux test with 1 mg. (0.1 cc. of a 1:100 dilution) of old tuberculin, or of a second strength solution (0.005 mg.) of tuberculin P.P.D., should be carried out. If there is a discrepancy, the Mantoux reaction is regarded as the decisive one (Vollmer and Goldberger¹⁷⁷³). Kereszturi¹⁷⁷⁸ reviewed the literature concerning the tuberculin patch test and found that the combined data show that 15 per cent of the Mantoux-positive subjects had a negative patch test, while 3 per cent of the Mantoux-negative

portion of the adhesive becomes loose, it must be immediately covered by a fresh piece, as close contact between the skin and the patch is required. The patch is removed after forty-eight hours, the test is read at that time, and again after another forty-eight hours.

The ophthalmic (Wolff-Eisner, Calmette), the nasal (Dupont and Milner), and the urethral tests (Oppenheim) are scarcely ever used at present.

In addition to the local reaction, focal and general manifestations not infrequently appear after tuberculin testing. Numerous authors—Doerr for one—consider the tuberculin



TUBERCULIN PATCH TEST



FIG 231 Eczematous reaction, rarely encountered

FIG 230 Typical papular reaction to epidermal application of old tuberculin (Vollmer test)

persons gave a positive one. In a series of several hundred cases, Pascher and Sulzberger¹⁷⁷⁹ found that the patch test corresponded uniformly with reactions to Mantoux (intra-dermal) tuberculin tests. The reactions were vesicular, papular, or vesiculopapular; in a few instances maculopapular and, in one, psoriasiform responses were observed. Certain technical factors are, however, of importance in avoiding poor results. The patch test area must be kept absolutely dry. If any

reaction to be of diagnostic significance only when it includes a focal reaction, for, these authorities hold, only the latter offers concrete evidence of the tuberculous character of a disease. In pulmonary conditions, a dose capable of calling forth such a focal response is, of course, dangerous; in cutaneous and bone tubercloses, however, the procedure may safely be employed, so long as the lungs are not involved. In cases of suspected skin tuberculosis, the perifocal tuberculin test (Strassberg) can be diagnostically helpful; if tuberculin injected into the periphery of a skin lesion evokes a much stronger reaction

¹⁷⁷³ Ibid 57, 1772, 1939

¹⁷⁷⁸ KERESZTURI, C. *Am Rev Tuberc* 44, 94, 1941.

¹⁷⁷⁹ PASCHER, F., and SULZBERGER, M. B. *Arch Dermat & Syph* 49: 256, 1944

than an injection into an unaffected skin site the lesions are presumably tuberculous

According to Volk tuberculin tests performed on skin sites previously exposed to natural sunlight or artificial quartz light irradiation elicit relatively weaker reactions. On the other hand relatively stronger responses are evoked in skin sites previously irradiated with grenz (Bucky) or roentgen rays (Konrad¹⁷⁶⁰ observations by the senior author)

Although it is impossible to differentiate between human and bovine tuberculosis by means of intracutaneous tests with the corresponding tuberculins this can apparently be done with avian tuberculin in cases of avian tuberculosis. Thus the senior author¹⁸⁰ has

tenuated bacilli and tuberculin. Unfortunately however we do not as yet possess anything like a dependable specific method although some gratifying results have been reported. Choucroun⁸ has reported the presence in a paraffin oil extract of heat killed tubercle bacilli of a sensitizing substance capable of protecting animals against tuberculosis. Tuberculin is sometimes of value in the treatment of skin tuberculosis. In the presence of a specific positive anergy in which the tuberculin reaction is negative repeated subcutaneous injection of a mixture of animal serum and tuberculin will according to Gans⁹ produce positive tuberculin reactions (method of conjugation) and thereby render



FIG. 232. ULCERATIVE REACTION TO AVIAN TUBERCULIN

Intracutaneous test with 0.1 cc of 1:1,000,000 dilution in patient with avian tuberculosis. Reaction to old tuberculin (1:10,000 dilution) was negative.

observed a number of such cases failing to react to old tuberculin but responding to avian tuberculin with exceedingly strong local manifestations (FIG. 232). It should be noted however that such a positive avian tuberculin reaction in the presence of a negative old tuberculin test is to be evaluated as strong evidence but not as definite proof; the final diagnosis must await the outcome of the animal inoculation (pathogenicity for the chicken).

In conclusion just a few words about specific therapy in tuberculosis. Throughout many long years attempts have been made to perfect a specific method for treating tuberculosis (with killed tubercle bacilli at

the organism sensitive to tuberculin). Another method suggested by Konrad¹⁷⁶⁰ is to irradiate certain skin sites with Bucky's grenz rays or with roentgen rays and on the following day to inject tuberculin well within the irradiated sites. The altered reactivity thus achieved is by no means restricted to the irradiated areas but is demonstrable after a while in far distant sites.

For the treatment of lupus vulgaris Richter exposes the affected areas to ultraviolet light and then applies a 50 per cent tuberculin ointment to these areas by inunction. The senior author achieved even stronger specific reactions by preceding this treatment with intravenous injection of 5 cc of 2 per cent acrid

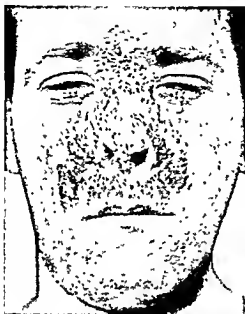
¹⁸⁰ CHOUCROUN. N. S. 98: 327, 1943.

¹⁸¹ GANS. O. Muenchen med. Wchnschr. 72: 139, 1927.

flavine, as suggested by Kerl, in order to increase the patient's reactivity to light (Figs. 233, 234)

The mechanism of the therapeutic effect of tuberculin in ocular tuberculosis has been the subject of considerable disagreement, but the intensive animal experiments of Woods^{175a} indicate that tuberculin desensitization has a favorable influence on both the incidence and severity of the disease Brown, Irons, and

cur in an organism that has been infected for some time Still more convincing are the subsequent disease symptoms that occur in wave-like attacks, the swelling of the lepromatous lesions, the erysipelas-like involvement of large areas of skin, the partial retrogression following such attacks—all these symptoms are analogous, as Jadassohn points out, to the manifestations following strong reactions to tuberculin Pardo-Castello and Tiant^{175b}



COMBINED TUBERCULIN AND ULTRAVIOLET THERAPY OF LEPROS VULGARIS

FIG 233 Appearance on admission to hospital



FIG 234 Eight weeks later after treatment twice weekly with minimal erythema dose of quartz lamp irradiation ten minutes after intravenous injection of trypanflavine, and localunction next day of 50 per cent tuberculin ointment

Rosenthal^{79b} reported a beneficial effect in two cases of tuberculous iritis of the repeated inhalation of the fumes of boiling suspensions of tubercle bacilli

2. LEPROSY

Credit goes to J. Jadassohn^{79a} for having pointed out that the variety of pictures observed during the course of leprosy is attributable to underlying allergic mechanisms. He even interprets what appear to be acute eruptions as due to sensitiveness, because they oc-

cur in an organism that has been infected for some time Still more convincing are the subsequent disease symptoms that occur in wave-like attacks, the swelling of the lepromatous lesions, the erysipelas-like involvement of large areas of skin, the partial retrogression following such attacks—all these symptoms are analogous, as Jadassohn points out, to the manifestations following strong reactions to tuberculin Pardo-Castello and Tiant^{175b}

^{175a} WOODS, A. C. *Pennsylvania M J* 46: 1133, 1943

^{175b} JADASSOHN, J. *Lepros Handb d path Mikroorg* (ed 3) 5, 1063, 1928

^{175c} PARDO-CASTELLO, V., and TIAN, F. R. *J A M A* 121: 1264, 1943

clinical picture of central healing and peripheral extension

The J. Jadassohn-Lewandowsky law (see p. 446) applies to leprosy as well as to other chronic infectious diseases during the phase in which great numbers of bacilli are present in the tissues, the histologic picture is one of a banal inflammation, distinguished only by the presence of numerous leprosy cells. During this period, in which—according to the aforementioned law—antibodies are still quite scant, the lepromin reaction (see below) is negative. This so-called tuberculous stage persists—unlike the corresponding stage in tuberculosis—for a very long time, sometimes even for years, before changing and entering into the tuberculous stage. In the latter phase, relatively few lepra bacilli are present, but typical tuberculous structures are to be seen, and the lepromin reaction is now positive.

From the foregoing it will be seen that the various forms of leprosy manifest striking differences in their reactivity to lepromin, which is a sterilized and carbolized extract of lepromatous tissues rich in Hansen bacilli. The test is known as the Mitsuda reaction. According to Bargehr,¹⁷⁴⁶ cutaneous inoculations elicit the following results: (1) no reaction in subjects who have never come in contact with leprosy patients, (2) positive reactions in individuals who have been in contact with lepers for some time, but who are themselves perfectly healthy (staff and personnel in leper colonies, relatives of lepers, persons in leprosy countries), (3) no reactions in leprosy patients with demonstrable bacilli and symptoms of existing leprosy, (4) positive reactions in individuals who, either briefly or for some time, were afflicted with leprosy, but in whom bacilli are no longer demonstrable; this group also includes patients with maculo-anesthetic leprosy, (5) positive reactions in individuals who have received repeated inoculations with lepromin, (6) in rare cases, strongly positive reactions during the first phase of the disease (i.e., eruption of severe erythemas). Expressed in another way, the lepromin test is negative in the lepromatous types of the disease, and the prognosis

is bad, while the test is strongly positive in the tuberculous types and the prognosis is favorable. In the non-specific types the result may be either positive or negative. Because of this as well as the fact that healthy contacts give positive reactions the test has no diagnostic value but is of great aid in the classification of cases of leprosy and in clarifying the prognosis (Pardo Castello and Tiant¹⁷⁴⁵).

All in all it may be said therefore that a negative skin test is an indication of the fact that there are very few, if any, specific antibodies in the organism, or that the available supply is insufficient to cope with the bacilli. A positive reaction, on the other hand, indicates that the antibodies have gained the upper hand in the struggle and are present in excess.

3. GLANDERS

Glanders is an infectious disease caused by *Bacillus mallei*. Two distinct clinical types are observed, the acute and the chronic. The discussion will here be restricted to the chronic form, since the acute commonly ends in death within about ten days. In chronic glanders, the altered reactivity of the skin of human beings and animals (horses, mules) is manifested by hypersensitiveness to mallein. In addition to the cutaneous allergy there is frequently a state of general allergy as well, for an intravenous or intraperitoneal injection of mallein quite often causes the death of the animal in anaphylactic shock (Nissl¹⁷⁴⁷). The skin reaction to mallein might well be the expression of an antigen-antibody reaction—a view supported by the fact that Nissl has reported passive transfer of the hypersensitiveness. Furthermore, the presence of complement-fixing antibodies has been demonstrated in the serum of patients. These antibodies are of great help in establishing the diagnosis of chronic and latent glanders in animals, and occasionally also in identifying the condition in human beings. The agglutination test, on the other hand, is not very reliable.

The immunity in glanders is quite similar to that in tuberculosis.

¹⁷⁴⁶ BARGEHR, P. München med. Wchnschr. 82: 56, 1935.

¹⁷⁴⁷ NISSL, J. Wien. tierärzt. Wchnschr. 3: 141, 1916.

4. RHINOSCLEROMA

Rhinoscleroma, belonging to the group of chronic infectious granulomata, must also be mentioned here. Soukoup, Boucek, Abramowicz and Biernacki, and Neuber¹⁷³⁸ succeeded in demonstrating that the specificity of the intracutaneous allergic response to an antigen prepared from scleroma cells is diagnostically useful. This is especially so in those cases in which the disease processes are confined to hidden or relatively inaccessible sites (making clinical and microscopic examinations difficult if not impossible), and those in which, for some reason or other, serologic tests cannot be performed. A positive reaction to 0.1 cc. of scleroma antigen consists in the appearance, after twenty-four hours, of an edematous hyperemic inflammatory area several centimeters in diameter at the site of the inoculation, it usually disappears after six to eight days and is replaced by a sharply circumscribed hard infiltration.

5. TULAREMIA

Foshay's¹⁷³⁹ intradermal test with formal-killed *Pasteurella tularensis* is of particular diagnostic value, since the reaction may become positive as early as the third day of the infection, while the agglutination test is never positive before the second week. The reaction is of the twenty-four- to forty-eight-hour tuberculin type, and is considered to be highly reliable. However, since the reactivity persists for years after recovery, the diagnosis of active disease should be considered only in the presence of suspicious lesions.

Foshay made the important discovery that patients who react positively to the bacterial material with a delayed papular lesion will exhibit an immediate response with wheal formation and erythema lasting about fifteen minutes when injected intracutaneously with antitularemia serum (0.04 cc. of a 1:10 dilution). Unlike all the other skin tests described in this chapter, the antibody is here injected to demonstrate antigen. A positive antiserum test may be regarded as specific provided that both an injection of normal serum from the same animal species, and an-

other injection of serum from the same animal species immunized against other organisms—these serving as controls—are negative. Unfortunately, the controls are positive in a high percentage of cases. This reaction becomes positive soon after infection—as early as eight hours after the initial chill—and persists long after recovery. The mechanism of this reaction is entirely different from that of the reaction to the bacteria; it is highly interesting, but not yet understood, and may in fact represent a new type of immunologic response or possibly a reversed passive anaphylaxis.

6. LYMPHOGRANULOMA VENEREUM

As shown by Frei,¹⁷⁴⁰ the presence of this disease, also known as lymphopathia venerea, lymphogranulomatosis inguinalis, and Durand-Nicholas-Favre disease, can be demonstrated by a specific allergic skin reaction to sterilized pus aspirated from an unruptured inguinal bubo. The positive reaction consists of an inflammatory papule with erythema; to be conclusive, the reaction must still be present after forty-eight hours (FIG. 235). Delayed reactions appearing after several days occasionally occur. Another specific test material is Lygranum. This material, prepared by inoculation of the causative virus into the yolk sac of the chick embryo, has proved to be highly useful. There is also available a preparation made from virus grown on mouse brain. Melczar and Sipos¹⁷⁴¹ performed passive transfer of the hypersensitiveness by means of both the Prausnitz-Kuestner and the Urbach-Koenigstein methods.

The Frei test first made it possible to establish the pathogenic relationship between lymphopathia venerea and rectal strictures.

Once the Frei test has become positive, it generally remains so for life; by itself, therefore, a positive test cannot be interpreted as proof of an existing disease, unless confirmed by the presence of clinical signs. It is also not infrequently observed that repeated tests render the patient's skin sensitive to the Frei antigen, so that subsequent tests elicit positive reactions even in the absence of the dis-

¹⁷³⁸ NEUBER, E.: *Wien. klin. Wchnschr.* 46: 935, 1933.

¹⁷³⁹ FOSHAY, L. J.: *Infect. Dis.* 51: 286, 1932; 59: 337, 1936.

¹⁷⁴⁰ FREI, W.: *Klin. Wchnschr.* 4: 2145, 1925; 6: 2042, 1927.

¹⁷⁴¹ MELCZER, M., and SIPOS, K.: *Dermat. Ztschr.* 78: 249, 1933.

ease. Positive reactions have been reported in cases infected with antigenically related viruses, such as those of psittacosis, meningo-pneumonitis, trachoma, inclusion blennorrhœa and certain strains of atypical pneumonia virus.

Although the test is rather specific it has the disadvantage of becoming positive relatively late—usually not until the skin begins to fuse with the inflamed glands. It is unwise, therefore, to draw any conclusions from a negative Frei test made shortly after the swelling of the glands appears. Moreover, unmistakable cases have been reported with negative reactions to potent antigens. In such cases the so-called inverted or reverse Frei test may be useful. This test method consists of taking pus from the patient's bubo

syphilis or whether the state of resistance is restricted to the site of inoculation (chancere immunity of Kolle¹⁷⁹⁴), is obviously of the greatest importance although not as yet conclusively settled. If there is no such thing as true immunity to syphilis then the objection that chemotherapy in the early stages prevents the development of immunity is refuted. However, old clinical observations as well as more recent experimental work, seem to confirm Chesney's views.

The failure of passive immunization with serums from syphilitic men or animals and the equally unsuccessful attempts actively to immunize against this infection suggest that resistance in syphilis depends not on humoral but on cellular factors. Apparently infection with virulent material is required to produce



FIG. 235. POSITIVE FREI REACTION FOR LYMPHOGRANULOMA VENEREUM.

heating it to 60 C for two hours, and inject it intracutaneously in an individual giving a positive Frei test. This method is analogous to Tréche's reaction for variola (see p. 453). This reverse method is said, however, to be less specific than the original Frei test.

Lastly, there is Sonck's⁷⁹⁹ interesting observation that 42 patients with lymphogranuloma venereum presented symptoms of light dermatitis without ever having received drugs that might have caused the condition. No satisfactory explanation is available. It can only be said that while most of Sonck's cases of this form of light hypersensitiveness were women, the one case seen by the senior author was a man.

7 SYPHILIS

The question as to whether, as Chesney¹⁷⁹³ holds, a true active immunity develops in

immunity. The immunologic conditions in syphilis are similar, in many respects, to those in tuberculosis.

The pathologic clinical and serologic manifestations of the various stages of syphilis may readily be understood as corresponding to the laws of allergy governing the course of infectious diseases. The diversity of the manifestations is due to the individual differences in the interplay between the *treponema* and the infected organism. The local expression of resistance on the part of the organism—the primary lesion or chancre—appears only after the spirochetes have had time to multiply to a certain extent in the site. From the biologic viewpoint the induration is to be regarded not only as a disease process but at the same time as a defense measure, however inadequate, in the course of which a considerable number of spirochetes are destroyed. During this process antisubstances are already being

⁷⁹⁹ SONCK, C. E. *Acta dermat. venerol.* 20: 529, 1939.

¹⁷⁹³ CHESNEY, A. M. *Harvey Lect. ser. 25: 1929-1930*. South M. J. 29: 1230, 1936.

¹⁷⁹⁴ KOLLE, W. and FRIGGE, R. *Med. Klin.* 30: 46, 1934.

formed, and their presence is evidenced by an altered reactivity to reinfection. About the eleventh day after the development of the primary lesion, the organism can no longer be reinfected.

As regards the secondary manifestations, they are probably best explained by the fact that the spirochetes, having entered the blood stream and tissues, are there attacked and destroyed. This is particularly true as regards the skin, because it is especially rich in antibodies. Thus, the symptoms of secondary syphilis are, on the one hand, signs of active disease, and, on the other, manifestations of an immunobiologic defense mechanism. In cases of untreated syphilis, it is well known that the cutaneous manifestations disappear within a few months, and that the disease then enters into a latent phase. During this period, there is an increase in the number of spirochetes: those that have been inactive in isolated organs multiply, enter into reaction with specific antibodies, and thus bring on clinical recurrences. After a number of such episodes, the disease process ceases in some cases. In others, however, after variable lengths of time there appear manifestations that differ markedly from those of the earlier stages, notably in the tendency toward disintegration of tissue (gumma), or toward healing with scarring or atrophy, and these late recurring lesions are, as a rule, much larger than the earlier ones.

To explain the tertiary manifestations, it must be assumed in the first place that a decrease in the supply of humoral antibodies permits the proliferation of the micro-organisms. However, the tissues have, in time, developed their powers of resistance, probably by means of cellular antibodies, to such an extent that they can destroy the spirochetes—a process resulting in the formation of nodular infiltrations with a tuberculoid structure. A high degree of allergy characterizes the tertiary stage of syphilis and explains this striking phenomenon, namely, the severity of the local manifestations during a phase in which, as is well known, the number of spirochetes is relatively small, certainly as compared with the secondary stage. Another indication of the high grade of hypersensitiveness of the organism during the tertiary period, as well as in congenital syphilis, is the appearance of the positive luetin reaction (see below). On

the other hand, there may also be a negative anergy (see p 24) in syphilis, as can be seen from the fact that vast numbers of spirochetes are sometimes present in the myocardium of the congenitally syphilitic child without giving rise to any detectable tissue reaction.

Histologically, the J Jadassohn-Lewandowsky law (see p 446) also applies to syphilis: numerous organisms—banal inflammation, few organisms—tuberculoid structure. Both the paucity of spirochetes and the tuberculoid structures are characteristic of the cutaneous manifestations of tertiary syphilis.

Furthermore, during all three stages of syphilis, when experimental superinfection is carried out, there is always, both clinically and histologically, an altered reactivity to the spirochetes. As Finger and Landsteiner first pointed out, the syphilitic individual generally reacts to superinfection with the very manifestations that are characteristic of the stage in which the disease happens to be at the time: that is, in the primary stage the response is an induration that appears after a shorter incubation period and in definitely milder form than the initial chancre; in secondary syphilis the response is papular, in the tertiary stage the reaction takes the form of a gumma. The same is true in cases of late congenital syphilis, in which superinfection leads to a response in the form of gummatous nodules (Truffi).

The appearance, during the secondary stage, of the so-called "malignant syphilis," or precocious tertiarism, which is characterized by violent local manifestations in the form of severe and partly destructive cutaneous and visceral processes, is attributed by most authors, including Stokes and Beerman,¹⁷² to the unusual allergic behavior of the tissues of these patients. The extraordinary reactivity of the skin is also indicated by the fact that the luetin reaction is almost invariably positive in cases of this kind.

Interstitial keratitis in congenital syphilis is also regarded as an allergic phenomenon: as explained in some detail elsewhere, this may be regarded (1) as an inflammatory-allergic reaction of the cornea to local spirochetes that had remained dormant and now become

¹⁷²STOKES, J. H., and BEERMAN, H. Syphilis. In Tice, F. Practice of Medicine, Hagerstown, Md. Prior, 1941, vol. 3, p. 349.

active and thereby antigenic (Schieck¹⁷⁹⁶) or (2) as the reaction of the allergized cornea to antigenic spirochetal substances that have entered the blood stream (Igersheimer¹⁷⁹⁷).

Naturally, many attempts have been made to devise a method of determining the allergic state of a syphilitic organism at any given time by means of skin tests. Whenever Noguchi's luetin (which is composed of heat killed *Treponema pallidum* cultured in ascitic fluid agar) was used for this purpose, the results of the skin tests could not be interpreted as being in any way specific, since positive reactions were elicited in a considerable percentage of nonsyphilitic subjects. On the other hand, tests with organ luetin (extracted from syphilomata of the rabbit testis and known as luotest), performed under certain limited conditions, are specific. Thus, while there is no response to organ luetin in the primary and secondary stages, the great majority of all cases of acquired syphilis in the tertiary stage, as well as almost all patients with congenital syphilis and "malignant syphilis," give positive reactions. In other words the test elicits responses particularly in those types in which, as demonstrated above, a high grade of allergy is demonstrable. In this connection it is interesting to note that a strong reaction to organ luetin may change the serologic reaction from negative to positive in tertiary cases in which there once were gummata (Mueller and Stein). The difference in the results obtained from the use of virulent *Treponema pallidum* taken from acute testicular syphilomas of rabbits, and suspensions of cultured spirochetes, is not difficult to understand, since the latter have undergone dissociation with a change in their antigenic properties (Kolmer¹⁷⁹⁸).

It has been mentioned that certain conditions must be strictly observed in order to endow the organ luetin reaction with specificity. As Sherrick¹⁷⁹⁹ has shown, it is possible to elicit a nonspecific positive luetin reaction, both in syphilitics who otherwise give a negative luetin test and in nonsyphilitics, when potassium iodide is administered prior to the

test. Similarly, the senior author¹⁸⁰⁰ was able to evoke nonspecific reactions to luotest in normal individuals if they had previously taken sodium iodide or sodium bromide in doses of 3 Gm a day for one week. It is imperative therefore that the patient take no great quantities of halogens during the two weeks preceding the performance of the skin tests. Furthermore, control tests must always be performed, for as Kolmer¹⁸⁰¹ and Stokes¹⁸⁰² have pointed out, a number of nonspecific substances may produce skin reactions in luetics indicating that the skin of such patients is more reactive than that of normal healthy individuals. By carefully performing the necessary controls, the senior author was able to use luotest for diagnostic purposes.

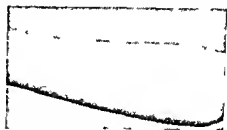


FIG 236 POSITIVE REACTION TO ORGAN LUETIN

The luotest reaction (FIG 236) appears as a sharply demarcated definitely elevated erythematous area of about 3 by 5 cm which reaches a maximum after forty eight hours. Nonspecific reactions are usually macular, not clearly defined, and disappear completely within forty eight hours. When the reaction is rapid and unusually large, the possibility of hypersensitiveness to rabbit protein should be considered (Brandt and Konrad).

An important question in connection with the immunologic aspects of syphilis is whether or not the positive Wassermann reaction may properly be considered as a serologic expression of the organism's capacity to produce antibodies to spirochetes. When complement fixation in syphilis was discovered by Wassermann it was assumed to be a specific reaction between the syphilitic antibody and the *Spirochaeta pallida* present in the extracts of

¹⁷⁹⁶ SCHIECK F. Deutsche med. Wochenschr. 40: 890 1914

¹⁷⁹⁷ IGERSHIMER J. Arch. f. Ophth. 8: 361 1913

¹⁷⁹⁸ KOLMER J. A. Arch. De. mat. & Syph. 4: 459 1942

¹⁷⁹⁹ SHERRICK C. W. J. A. M. A. 65: 404 1915

¹⁸⁰⁰ URBACH E. Zentralbl. f. Haut u. Geschlechtskr. 35: 39 1911

¹⁸⁰¹ KOLMER J. A. MATSUNAMI T. and BROADWELL S. JR. J. A. M. A. 67: 718 1916

¹⁸⁰² STOKES J. H. ibid. 68: 1092 1917

syphilitic tissues employed as antigens. However, when it was found that saline and alcoholic extracts of normal mammalian tissues served equally well as the antigen in the test, the assumption that the Wassermann reaction represented a specific antigen-antibody reaction was largely abandoned, and the suggestion was advanced that the reaction was biologically nonspecific. After the successful cultivation of the organism by Noguchi, complement fixation studies with spirochete cultures were again performed, and indicated that, in addition to the antibody that reacts with the tissue lipids in the Wassermann and the flocculation reactions, a true antibody is produced in syphilis, reacting specifically with spirochetes. Kolmer,¹¹⁹³ who recently summarized the extensive literature as well as his own important experimental work, is of the opinion that the results of agglutination and complement fixation tests with suspensions of virulent *Spirochaeta pallida* obtained from acute testicular syphilomas in rabbits very definitely indicate the production of antibodies. However, Kolmer and Tuft¹¹⁹⁴ do not regard the positiveness of these reactions as an indication of immunity in syphilis, but rather as an index of the degree of infection. In short, the evaluation of the Wassermann reaction strictly from the physical and chemical viewpoints has again been abandoned, and the present consensus is that the reaction is based on a specific process—i.e., on an underlying antigen-antibody reaction. Some are now of the opinion, particularly on the basis of Klopstock's experimental work, that positive serologic reactions are the expression of an immunologic process directed exclusively against the invading lipid-containing spirochetes. Another theory, advanced by Sachs, is that certain chemical changes in the blood in syphilis are the expression of an antigen-antibody reaction, with autogenous lipids—liberated as the result of the disease—as the hapten, and the spirochetal proteins as the carrier substance.

Sulzberger¹ explains the fact that substances other than the products of the treponema itself can be used as antigens in serologic reactions, on the basis of the heterophile mechanism—i.e., the antigenic constituents of the heart, muscle, and brain of various species of

animals are immunologically related to the antigens in the treponema.

The allergic viewpoint has assumed special significance in antisyphilitic therapy. The most important question to be answered is whether modern methods of treatment—particularly the use of arsenicals—do not unfavorably influence the natural defense powers of the syphilitic patient. The leading syphilologists, including Stokes, Moore, Pusey, Chesney, and Kolmer, are unanimously of the opinion that if antiluetic treatment is not followed through to completion, the patient is left both without cure and without defense. "Treatment just sufficient to heal the chancre and secondary lesions, but insufficient for biologic cure, is therefore more harmful than no treatment at all, because of a reduction in acquired resistance" (Kolmer and Tuft¹¹⁹⁴). Authorities such as Pusey and Finger have pointed out that the too rapid disappearance of the cutaneous symptoms is likely to interfere with the formation of antibodies, and thus to further the development of para- and metasyphilitic disease processes, particularly vascular and central nervous system involvement. Furthermore, Stokes points out that arsphenamines, inadequately used, may leave the patient not only without defense, but in a state of allergic hypersensitiveness akin to the altered reactive capacity of tertiary syphilis.

The principles of immunity are, therefore, of fundamental importance in planning the treatment of syphilis. The therapy must be continuously carried out until the point of complete sterilization is attained, if possible. A comprehensive critical review of the problems of immunity and allergy in syphilis was recently contributed by the senior author in collaboration with Beerman.¹³⁰³

Numerous attempts have been made to eliminate the general state of anergy commonly arising in metasyphilis, by means of immune-therapeutic measures. These attempts have included specific as well as non- and metasppecific methods. The latter approach was conceived by Wagner-Jauregg, who first tried to overcome the anergy by enhancing the defenses of the organism, using

¹¹⁹³ URRICH, E., and BEERMAN, H.: *Am. J. Syph., Gen. & Ven. Dis.*, in press, 1946

tuberculin in large doses and subsequently malaria inoculations. The results obtained, particularly in paresis, are striking.

8 FUNGUS DISEASES

We shall have to limit the discussion here to the allergic manifestations caused by the most common fungi. During the past few years, medical mycology has grown in importance as a field of investigation, and the reader is referred to the excellent monograph by Lewis and Hopper¹⁹¹ for a more detailed treatment of the subject.

Elsewhere in this book, brief mention has been made of the problem of dividing fungi into categories. Here it need only be mentioned that the most important subdivision is that of the hyphomycetes, or fungi imperfecti, since most of the human pathogens fall into this group. Those that cause skin diseases are commonly classified as dermatophytes.

a) DERMATOMYCOSES

The immunologic conditions in fungous diseases are quite comparable to those in tuberculosis. Experimental studies with *Trichophyton gypsum*, for example, have shown that hypersensitiveness develops only during the course of an infection. The degree of hypersensitiveness rises gradually, reaching its peak some two or three weeks after the lesions are healed (de Lamater^{190a}). The allergy gradually decreases over a period of months after the infection.

Bloch^{190b} demonstrated, first by means of animal experiments and then in human beings, that once an individual has recovered from a fungous disease the entire skin surface, including the clinically unaffected areas, acquires a state of specifically altered reactivity, as evidenced by a more rapid and less intense reaction to reinfection. Studies of repeated reinoculations performed on animals at intervals after the primary inoculation, have revealed that reinoculation as early as the fifth day elicits nothing more than an abortive reaction, and on the eighth day no response

whatever. The acceleration of the process, evidenced by the early reaction, can be verified both clinically and histologically.

In human beings also following either a spontaneously acquired or an artificially induced initial infection, the skin manifests a similarly if not quite so markedly altered reactivity to reinoculation or to testing with trichophytin. The degree of the allergy, and thus the results of reinoculation or of cutaneous testing, are determined by the following factors: the relative virulence of the fungus causing the spontaneous mycosis or employed for the initial inoculation, the depth, extent, and degree of inflammation, and the number of the primary foci, and the patient's individual capacity for allergization.

As demonstrated by J. Jadassohn, the evolution, configuration, and involution of mycotic foci are largely dependent upon the immunologic state of the skin. When the allergy is strongly developed, the fungi may be directly destroyed, when it is of a lower degree, it serves only to inhibit the multiplication of the hyphomycetes, so that the fungi can again begin multiplying as soon as the immunity retrogresses.

Local variations in the degree of hypersensitiveness may very well be the explanation of the commonly observed corymbiform or iris shaped configuration of trichophytic lesions, while the refractory free zones that appear in or about healed foci may be regarded as an expression of local positive anergy. This local immunity is the reason for the spontaneous healing of the skin lesions.

As a rule, allergic hyposensitiveness of the integument is encountered only in deep inflammatory mycoses, though it may also develop in superficial conditions, provided they are of long standing. Furthermore, the allergization depends in part on the species of fungus. Animal hyphomycetes, for example, are more likely to sensitize than the human variety.

The highest degree of allergy is manifested by patients with trichophytids. (The remarks following will apply also to the other dermatophytids, such as microsporids, epidermophytids, and monilids.) As explained in more detail below (p. 782), the term "id" is understood to designate the reaction of the highly allergized skin to a hematogenously dis-

^{190a} LAMATER E. D. DE J. Invest. Dermatol. 4 143 1911

^{190b} BLOCH B. Allgemeine und experimentelle Biologie der durch Hyphomyceten erzeugten Dermatomykosen. Handb. d. Haut u. Geschlechtskr. 11 300 1923

tributed organism and/or its products. A trichophytid (FIG 237) is, therefore, a lesion that arises when the fungus is transported hematogenously from a primary trichophyton focus to the allergic skin (Bloch^{190a}). In general, fungi cannot be cultured from "id" eruptions, nor demonstrated microscopically. According to Peck, the mechanical factors of pressure and rubbing play an important part in bringing the fungous elements into more

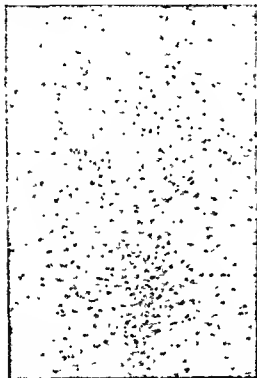


FIG 237 TRICHOPHYTID (LICHEN TRICHOPHYTICUS)
Occurring ten days after X-ray epilation in child with
deep trichophytosis of scalp

intimate contact with the deeper layers of the skin and probably forcing them into the blood stream. Indeed, under appropriate conditions, the presence of fungi in the blood can be demonstrated. Numerous authorities, including Lewis and Hopper,¹⁹¹ subscribe to the principle that a positive reaction to trichophyton is requisite to a diagnosis of dermatophytid.

The clinical criteria on which a diagnosis of phytid may be based are as follows:

The allergic phytid eruptions occurring in association with trichophyton infections are often generalized and are more likely to occur

in the deep-seated form of trichophytosis. They are often accompanied by constitutional symptoms such as mild elevation of temperature, lymphadenopathy, and splenomegaly. The most common form is the lichenoid trichophytid, which appears chiefly on the trunk and the extremities, in the form of small follicular red papules. These lesions may be disseminated or grouped, and, by confluence, may form plaques that resemble pityriasis rosea, psoriasis, or seborrheic dermatitis. Occasionally the eruption is scarlatiniform or morbilliform, and lesions resembling erythema multiforme or erythema nodosum have also been described. These eruptions usually run a short course, but recurrences are common.

Epidermophytic phytids may be generalized or localized, and usually occur in association with severe and acute attacks of epidermophytosis of the feet. The generalized form is uncommon, but when it occurs it is not unlike that caused by trichophyton. The localized form usually involves both hands, and is manifested by closely set groups of vesicles in symmetric distribution, associated with intense pruritus. These lesions may be superficial or deep-seated, and the accompanying inflammatory reaction varies with the degree of sensitiveness. Epidermophytids of the hands (FIG 238) often bear a close resemblance not only to acute dyshidrosis, from which it is often difficult to differentiate them, but also to contact dermatitis.

The experimental investigations of Peck^{190b} give additional support to Williams^{190c} concept that certain eczematous eruptions of the hands are trichophytids, secondary to fungous foci in the skin between the toes and in the toenails. We do not as yet possess any dependable clinical, histologic, bacteriologic, or allergic method for differentiating between eczematous dermatophytid and hand conditions such as eczematous contact-type dermatitis, eczematous staphyloid (G. Andrews), and eczematous drug eruption. Nevertheless, an acute eczematous outbreak of the hands, associated with an exacerbation of a dermatophytosis of the feet, is in all probability an "id" eruption, provided that fungous

^{190b} PECK, S. M. Arch. Derm. & Syph. 22: 40, 1930

^{190c} WILLIAMS, C. M. Ibid. 13: 451, 1927

elements can be demonstrated in the lesions on the feet and that the reaction to trichophyton is strongly positive

The development of a generalized dermatophytid eruption usually depends not only on the presence of a local inflammatory mycotic infection but also on one of two nonspecific factors—roentgen irradiation of the primary focus for therapeutic purposes or the injection of trichophyton for diagnosis. Not infrequently the history reveals that both of these measures were carried out. This effect of the roentgen irradiation might be attributed to its tendency to heighten the inflam-

matization with fungus extract may be tried

It is generally assumed that the immunologic mechanisms underlying mycotic allergization are explainable on the basis of antibodies partly cellular and partly humoral. Thus Martenstein was able to demonstrate specific antibodies in the skin of guinea pigs sensitized to the fungus. Furthermore Jessner and Hoffman found that the blood of patients with trichophytosis contained antibodies that inhibited the growth of fungi while Engwer found substances corresponding to the antituberculin in tuberculosis.

Sulzberger and Kerr¹⁶⁰³ demonstrated an antibody to trichophyton by means of passive transfer. This work was confirmed by Tomlinson¹⁶⁰⁹ and in relation to experimental animals by Henrici¹⁶¹⁰

The altered reactivity of the skin in fungus infections can be shown by means of the extracts that were first prepared by Plato and Neisser in 1902 and that correspond to tuberculin. They are known as trichophyton microsporin epidermophyton and favin according to the respective fungi.



FIG. 238 EPIDERMOPHYTID

Vesicular eruption of hands in patient with recurrent epidermophytosis of feet. Lesions were sterile on culture.

mation of the primary focus thus increasing the absorption of the fungus or their toxins. In this connection it has been shown in superficial microsporin infections that patients who previously had been negative to microsporin or trichophyton tests reacted positively after roentgen epilation. The change was found to take place approximately two weeks after exposure to the roentgen rays.

Dermatophytids do not respond to direct antiparasitic treatment. The only effective treatment consists in local therapy of the primary sites of infection usually between the toes. After a while a very cautious hypo-

TECHNIC The intradermal test is generally performed with 0.1 cc. of a 1:30 or 1:50 dilution and should be observed for the occurrence of a reaction after ten or fifteen minutes for an immediate wheal reaction, after forty-eight hours for a delayed reaction and again at the end of one week for a sustained reaction. The test most commonly elicits a delayed local reaction in the form of a dark red papular induration about 1 cm. in diameter surrounded by an erythematous halo (Fig. 239). In cases of very marked allergy, particularly in deep inflammatory trichophytosis, the reaction not uncommonly takes the form of local vesiculation and sometimes even of a necrosis. In addition there may be lymphangitis leading to the regional lymph nodes which may be enlarged and inflamed. Moreover in some occasional instances the intradermal reactions even in apparently superficial and not especially widespread dermatomycoses may give rise to ichenoid or miliary vesicular eruptions and sometimes even to systemic manifestations (Templeton¹⁶⁰⁸ Urbach and Stern¹⁶¹¹). Ramirez¹⁶¹² observed asthma, sneezing and hives following an intradermal inject of trichophyton. It is advisable therefore in conditions that are spreading or in the inflammatory

¹⁶⁰³ SULZBERGER, M. B. and KERR, P. S. *J. Allergy* 2: 11, 1930.

¹⁶⁰⁴ TOMLINSON, W. J. *ibid.* 6: 373, 1935.

¹⁶⁰⁵ HENRICI, A. T. *Proc. Internat. Cong. N. obol.* 1949, p. 367.

¹⁶⁰⁶ TEMPLETON, H. J. *J. Allergy* 5: 521, 1934.

¹⁶⁰⁷ URBACH, E. and STERN, B. A. *Arch. Dermat. & Syph.* 41: 983, 1948.

¹⁶⁰⁸ RAMIREZ, M. A. *M. J. & R.* 132: 342, 1930.

stage, to perform the initial skin test with a 1:500 dilution, followed by a test with 1:100 strength on the next day, and then to proceed to the 1:50 concentration.

Lewis and Hopper¹¹ have defined the following standards for reading the results of delayed or sustained reactions in much the same way as the American Tuberculosis Association grades tuberculin tests plus-minus (\pm) for an area of slight erythema approximately 5 mm. in diameter, 1 plus (+) for a reaction from 5 to 10 mm. in diameter, 2 plus (+ +) for a response from 10 to 15 mm. in diameter, 3 plus (+ + +) for an area from 15 to 20 mm. in diameter, and 4 plus (+ + + +) for an elevated area of reaction 20 mm. or more in diameter.



FIG 239 POSITIVE REACTION TO INTRACUTANEOUS INJECTION OF 0.1 CC OF TRICHOPHYTIN (1:50 DILUTION)

While the delayed or tuberculin-type skin reaction is the typical response, there is in rare instances an immediate wheal reaction (Marcussen¹²). Vaughan¹³ is of the opinion that the latter is more likely to occur in inhalant allergy due to fungous sensitization, but it was also found in cases of dermal manifestations. The nature and significance of the immediate cutaneous reactions are not as yet clear.

As shown in some detail elsewhere, the intracutaneous method has the disadvantage inherent in all very sensitive biologic tests—namely, that the results are far less specific than are those of cutaneous tests. The latter, conversely, are relatively inaccurate because of the varying rate of absorption of the extracts applied to the scarified skin.

In eczematous manifestations on the hands, with concurrent epidermophytosis of the feet, patch tests with trichophytin may be performed (Sulzberger and Lewis^{15,16}). The reac-

tion, which often appears only after several days, usually takes the form of a localized dermatitis presenting a histologic picture of spongiosis and vesiculation. However, the patch test with trichophytin is less delicate and less reliable than the intracutaneous method.

The interpretation and limitations of the positive trichophytin test are the same as in the case of tuberculin: the reaction may be the result of either a present or a past infection. These tests, therefore, although generally specific, are very often of no diagnostic value. In this connection, it should be remembered that the incidence of fungous diseases is very high, especially in North and South America. In Europe, where "athlete's foot" is relatively less common, trichophytin is of distinct value in the diagnosis of active ringworm. Furthermore, the trichophytin test represents a group reaction in the majority of instances; for example, it is also positive in microsporic infection and epidermophytosis. Sulzberger's⁴ explanation is that extracts of hyphomycetes contain, in addition to allergenic factors that may be peculiar to each particular species, an allergenic principle common to all.

Therefore, while in a given case a positive trichophytin test is not in itself diagnostic, a fungous etiology may be assumed when it is supported by other findings. The prognosis is then favorable, and the treatment should be conservative. If, on the other hand, the test gives a negative result despite the presence of proved fungous infection, the immediate prognosis is poor, either because immunity has failed to develop or because the degree of immunity is inadequate, treatment should therefore be intensive and sustained. It is interesting to note, furthermore, that some fungi, such as *Trichophyton purpureum* or *Achorion schoenleinii*, have a low sensitizing index; the response to therapy in these cases is notoriously poor.

A test may of course be negative in a case of recent infection in which sensitization has not had time to develop. On the other hand, if the intracutaneous test to trichophytin is negative, and neither microscopic nor cultural studies reveal the presence of fungi, an exudative inflammatory reaction may be considered as nonmycotic.

¹¹ MARCUSSEN, P. V., Arch. Dermat. & Syph. 36: 494, 1935.

¹² SULZBERGER, M. B., and LEWIS, G. M. Ibid. 22: 417, 1930.

As to the therapeutic efficacy of fungous preparations there is considerable divergence of opinion. On the basis of the available evidence it may be said that specific anti-allergic treatment apparently improves the results of topical treatment and considerably shortens the course of the deep forms of mycotic disease and of general eruptions. In other words the specific approach is of value in those types in which the immunologic behavior of the organism is altered in the direction of an increased reactivity. On the other hand it is almost worthless in the very forms in which its help would seem to be most required—the torpid, the superficial and the eczematoid forms. This is not at all surprising from the allergic point of view, since there is virtually no antibody formation in these latter types. It is hoped that at some future date it will be possible to manage these cases by means of active immunization (stimulating the tissues to the formation of antibodies possibly with the aid of conjugate protein antigens). On the other hand Miller and his associates¹⁸ advocate the use of undenatured trichophyton antigen. According to these authors the undenatured trichophyton stimulates the formation of complement fixing antibodies and precipitins.

The investigations of Da Fonseca^{18,17} and particularly those of Peck¹⁸ may perhaps be helpful in regard to this problem. These authors were able to prepare trichophyton fractions in which no skin test principle could be demonstrated—not even in individuals who were markedly sensitive to trichophyton—but that were extremely effective in producing rapid desensitization in suitable patients without eliciting any local or focal reactions. These experiments suggest that the skin test factor is not necessarily identical with the desensitizing principle.

The contributory role of fungous (and other) infections in the production of hypersensitivity to other agents such as drugs and chemicals was especially emphasized by Stokes and Kulchar.²⁰ According to Wise and Sulz-

berger^{20,1} and Beerman^{4,7} antecedent ring worm infections can pave the way for a subsequent contact dermatitis since the continuity of the skin is interrupted by the infection thereby permitting the entry of the second sensitizing substance. The combination of the two allergens then exceeds the level of tolerance. On the other hand there is a possibility that the conjugation of the fungus acting as a carrier substance with the chemical acting as a hapten is responsible for the additional allergization. Thus Haxthausen succeeded in producing experimental allergization to mercury compounds by inunction of the latter substances into mycotically infected skin sites.

The synergistic action of fungi and contactants is becoming increasingly important in relation to industrial dermatoses as well as to contact dermatitis of the hands and feet (e.g. due to sock dye, shoe leather and gloves). Some dermatologists and allergists go so far as to hold that epidermophytosis of the feet or groins even in the absence of id eruptions may predispose to contact dermatitis when the patient is in an allergic state as indicated by a positive trichophyton test. Downing^{4,7} states that while many cases of occupational dermatitis are merely aggravations of previous mycotic infections, sensitization due to distant fungous infection such as that on the feet may be an important factor in the precipitation of certain types. Norwood and Evans³ described leather phytids due to a combination of hypersensitivity to leather gloves and an allergization of the hands from dermatophytosis elsewhere (usually on the feet). Kammer and Callahan¹⁵ reported 22 cases of dermatitis due to contact with torch oil (crude kerosene) on the hands of men sensitized by a superficial mycotic infection.

On the other hand in the experience of Peck, Botwinick and Schwartz^{20,1} dermatophytosis contrary to popular opinion did not appear to be an important predisposing cause in industrial contact dermatitis. Cases of allergic contact dermatitis showed no higher incidence of dermatophytosis or of positive reactions to trichophyton than did controls.

¹⁸ MILLER H. E. *ibid* 44: 804, 1941.

¹⁷ FONSECA O. DA J. R. AREA LEAO A. E. DE GONSALVES BOYAPOGO N. and RABELO J. R. *Rev. med. c. do Bras.* 144: 31, 1936.

¹⁸ PECK S. M., GLICK A. and WEISSBERG E. A. *ibid* *Dermat. & Syph.* 44: 816, 1941.

¹⁵ KAMMER A. G. and CALLAHAN R. H. *J. A. M. A.* 109: 1511, 1937.

b) MONILIASIS

In cases of intertrigo of the inguinal, submammary, and interdigital regions, in which *Odium albicans* (*Monilia albicans*) was present, Ravaut¹⁵²⁰ observed that quite commonly erythematous lesions appeared after some time and that no fungi could be demonstrated in them. These skin manifestations were not unlike Brocq's psoriasiform parakeratosis, and may be described morphologically as somewhere between dermatitis and psoriasis. It was found, moreover, that the eczematoid areas cleared as the intertrigo regressed, reappearing when the primary lesions again erupted. The injection of oidiomycin (known as levurin abroad), a fungous extract prepared in the same way as trichophytin, was frequently found to elicit not only a dermatitis-like local reaction that clinically and histologically corresponded to the primary lesion, but also a flare of the secondary eczematoid skin manifestations. As to therapy, intensive treatment of the primary foci sufficed to bring about the disappearance of the secondary eruption. According to Ravaut, these clinical, parasitologic, biologic, and therapeutic observations warrant the conclusion that intertrigo caused by yeasts and the dermatitic lesions described above are pathogenetically related, and that the latter are to be regarded as moniliids or levurids.

Ramel¹⁵²¹ performed patch tests with oidiomycin, stressing the eczematoid nature of the reactions elicited. He is of the opinion that at least some cases of so-called microbial eczema are attributable to yeast infection.

According to Peck,¹⁵²² the oidiomycin test is rarely positive in infants and children, but in progressively older age groups gradually reaches an incidence of almost 100 per cent of positive reactions. Therefore, although the oidiomycin reaction is specific, it is of no diagnostic value in adults. Oidiomycin elicits a response of the tuberculin-like delayed type.

In a case of severe pulmonary moniliasis, Hiatt and Martin^{1523a} were unable to elicit a reaction with an autogenous *Candida albicans* vaccine, but intracutaneous injection of

specific immune rabbit serum produced a wheal with pseudopodia. Since the agglutination test was negative, it was thought that there was an excess of antigen in the tissues and an absence of circulating antibodies. The administration of small amounts of immune rabbit serum resulted in a dramatic recovery, accompanied by the appearance of agglutinins in the serum and a slightly positive skin test to the vaccine.

c) ACTINOMYCOSIS

Neuber¹⁵²², Gougerot, and others reported that patients with actinomycosis respond with strongly positive skin reactions to intracutaneous



FIG. 240 SKIN TESTS WITH ACTINOMYCOSIS VACCINE

a = positive reactions forty-eight hours after intracutaneous injections of decreasing concentrations in a case of actinomycosis (at top, control with saline solution) b = minimal erythema in normal control in response to same concentrations (Courtesy Dr E. Neuber)

ous injections of a filtrate of old broth-cultured actinomycosis fungi, killed in an autoclave. This reaction is specific and diagnostically useful (Fig. 240). Furthermore, this preparation is of therapeutic value.

¹⁵²⁰ RAVAUT, P. and RABEAU, H. *Presse méd.* 37, 372, 1929

¹⁵²¹ RAMÉL, E. *Rev. méd. de la Suisse Rom.* 49, 887, 1929, *idem* and BENZIGER, A. *Klin. Wchnschr.* 9, 2435, 1930

¹⁵²² PECK, S. M. *J. Allergy* 11, 309, 1940

^{1523a} HIATT, J. S. and MARTIN, D. S. *J. A. M. A.* 130, 205, 1946.

^{1523b} NEUBER, E. *Wien. Klin. Wchnschr.* 45, 357, 1932.

CHAPTER XIX

PARASITIC AGENTS

ALLERGY produced by parasitic agents may properly be called infestation allergy, in contradistinction to infectious allergy, which is induced by bacteria or viruses. The parasitic allergen is either the tissue protein or the excretory products of helminths, particularly the echinococcus, ascaris, trichinella, strongyloides, schistosoma, and the oxyuris. The presence of infestation allergy can be determined by allergic skin tests, by complement fixation and precipitin reactions, and, rather rarely, by clinical allergic manifestations.

Extensive investigation by Fuelleborn¹⁸²⁴ and other authors revealed that the prolonged presence of roundworms and flatworms in the body of the host causes allergization of the skin and mucosa. This is demonstrated by the fact that inoculation of the skin with minute traces of material of the body of the given parasite evokes marked local wheal formation, as well as by the fact that application of the extract to the mucosa elicits clinical symptoms (asthma or rhinopathy).

We must hasten to add, however, that positive skin reactions almost invariably represent group reactions, for example, a positive skin test with ascaris antigen may indicate nothing more than the presence of nematodes. An other disadvantage detracts from the practical usefulness of these skin tests although positive skin reactions, if confirmed by adequate controls, may be regarded as specific, the reactivity may persist for years and even decades after the disease has been cured. In addition, it is well to remember that the diagnostic value of the trichinella and other tests diminishes with repeated intracutaneous injections (Baron and Brunner¹⁸²⁵).

Despite these definite limitations, the Casoni reaction, in which hydatid fluid is used as the antigen for demonstrating the presence of echinococci, has gained widespread recognition. Since the Casoni reaction is group

specific and since human hydatid fluid is often difficult to obtain Rose and Culbertson¹⁸²⁶ used rabbit cysticercus as the antigen, with good results, while Dennis¹⁸²⁷ prepared a dry stable antigen from echinococcal fluid obtained from sheep or cows. Aside from the immediate urticarial reaction described by Casoni, Botteri reported the appearance of a delayed papular reaction, the latter is said to be the more convincing evidence of the presence of an allergy. With serum taken from echinococcus carriers, Botteri was able to sensitize normal human beings by the passive transfer method, these individuals then responded to echinococcus antigen with a delayed reaction. This would seem to constitute proof of an antigen antibody mechanism underlying the delayed reaction here.

Skin tests with the trichinella extracts introduced by Bachman¹⁸²⁸ are of considerable aid in the diagnosis of trichinosis. The antigen used for this test is a 1:10,000 dilution of a saline extract of dried and powdered larvae of *Trichinella spiralis*, free from the tissue of the host in which the parasites developed. The skin test is performed in the usual manner by injecting 0.1 cc of diagnostic trichinella extract (Lilly, Parke, Davis) intradermally on the flexor surface of the forearm. A control solution of the extracting material is injected at the same time. Positive reactions are of two kinds—the immediate response which appears within twenty to thirty minutes as a central wheal surrounded by an area of erythema, and the delayed response, which may not become apparent until eighteen or twenty-four hours later. The significance of the latter is not entirely clear. It is said by McNaught¹⁸²⁹ to occur early in the infection (from the third to the tenth day of illness, i.e., before the immediate reaction can be elicited), or in long standing quiescent cases.

¹⁸²⁴ FUELLEBORN F. and KIRCH W. Arch f. Sch. Hyg. u. Tropen Hyg. 33 (suppl. 2) 168 1929

¹⁸²⁵ BARON B. and BRUNNER M. J. Allergy 13 459, 1942

¹⁸²⁶ ROSE H. M. and CULBERTSON J. T. J. A. M. A. 115 594 1940

¹⁸²⁷ DENNIS E. W. J. Parasitol. 23 62 1937

¹⁸²⁸ BACHMAN G. W. J. Prev. Med. 2 35 1928

¹⁸²⁹ MCNAUGHT J. B. Pacific Coast Med. 8 3 1941

Augustine and Theiler¹³³⁰ found the skin test in hogs more accurate than microscopic examination of muscle. According to McCoy et al.,¹³³¹ this method has an accuracy of 92 per cent in patients tested two to six weeks after the onset of infection. According to Gould¹³³² the immediate intradermal reaction may be elicited on the average for nearly ten years after the infestation. By way of comparison, the blood precipitin test remains positive for one or two years, and eosinophilia usually persists six months and rarely more than one year. About 5 per cent of the intradermal reactions were nonspecific in nature and were believed to be due to sensitization induced by antigenic material in nonviable trichinae present in ingested pork.

Unless it is accompanied by the clinical symptoms of trichinosis (e.g., fever, nausea, diarrhea, circumorbital edema, muscular pains) and considerable even though transient eosinophilia, the positive skin test does not have diagnostic value. If, however, the reaction is negative in the first days of the infection, but becomes positive after the third week, it carries a diagnostic message. On the other hand, a repeatedly negative skin reaction, accompanied by a negative test for precipitins in the blood serum after a month's illness, excludes the diagnosis of trichinella infestation. It is important to bear in mind that the skin test may be negative in severe, fulminating trichinosis, reflecting a state of negative energy. Moreover, cross reactions may occur as illustrated by the positive reaction in a case of cysticercosis reported by Kathe and Peters.

Bachman has reported a skin test with ascaris antigen (Lederle) to demonstrate the allergization of ascaris hosts. It should be remembered, however, that there is a common antigen in ascaris and trichina, and that it is much stronger in the former than the latter (Baron and Brunner¹³³³). The specificity of this skin test is, therefore, subject to some doubt, particularly in the absence of supportive evidence, such as the presence of ova or

larvae of the intestinal parasite. Positive skin test reactions were obtained by Brunner, Altman, and Bowman¹³³⁴ in dogs with existing or past naturally occurring nematode infestations. Moreover, their serums contained a heat-labile antibody capable of passively transferring the sensitiveness to other animals and even human beings.

According to Taliaferro and Hoffman,¹³³⁵ approximately 90 per cent of all cases of *Filaria bancrofti* infestations give positive skin reactions to tests with an antigen prepared from filaria from dogs' hearts. Because of this group specificity, Bozicevich and Hutter¹³³⁶ and Thompson et al.¹³³⁷ successfully employed *Dirofilaria immitis* extract, and Culbertson, Rose, and Demarest¹³³⁸ an antigen derived from *Litomosodes*, a filarial worm found naturally in the pleural cavity of the cotton rat. The latter also gave skin and complement fixation tests for loiasis and onchocerciasis.

Culbertson and Rose¹³³⁷ found that an extract prepared from *Pneumoneces medioplexus*, a fluke found in the lungs of frogs, contains an antigen which may be satisfactorily employed for specific skin tests in human schistosomiasis.

According to Toettermann,¹³³⁹ pernicious tapeworm anemia may be due in large part to an increasing sensitivity to tapeworm toxin. He bases this opinion on the observation that the parenteral administration of an alcoholic extract of tapeworm to two persons who had suffered from pernicious tapeworm anemia, resulted in an impairment of the blood picture, which improved spontaneously when the injections were discontinued. Some local and general symptoms were also observed.

Finally, the clinical manifestations of parasitic allergy remain to be considered. After spontaneous rupture, or following inadvertent puncture or surgical removal of echinococcus cysts from the abdomen or chest, the patient

¹³³⁰ AUGUSTINE, D. L., and THEILER, H. *Parasitology* 24: 60, 1932.

¹³³¹ MCCOY, O. R., MILLER, J. J., JR., and FRIEDLANDER, R. D. *J. Immunol.* 24: 1, 1933.

¹³³² GOULD, S. E. *Bull. New York Acad. Med.* 45: 444, 1945.

¹³³³ BARON, B., and BRUNNER, M. *J. Allergy* 10: 153, 1939.

¹³³⁴ TALIAFERRO, W. H., and HOFFMAN, W. A. *J. Prev. Med.* 4: 261, 1939.

¹³³⁵ BOZICEVICH, J., and HUTTER, A. *Am. J. Trop. Med.* 24: 203, 1944.

¹³³⁶ THOMPSON, K. J., RIFKIN, H., and ZARROW, M. *J. A. M. A.* 129: 1074, 1945.

¹³³⁷ CULBERTSON, J. T., ROSE, H. M., and DEMAREST, C. R. *Am. J. Hyg.* 39: 152, 156, 1944.

¹³³⁸ CULBERTSON, J. T., and ROSE, H. M. *ibid.* 36: 511, 1942.

¹³³⁹ TOETTERMAN, G. *Acta med. Scandinav.* 118: 422, 1945.

not uncommonly responds with a shock that is sometimes lethal, and that Chauffard, Boidin, and Laroche regarded as an anaphylactic phenomenon. More recently, however, some doubt has been expressed (Doerr) as to whether this is truly an anaphylactic reaction, since it is believed that the cyst contents possess a primary toxic action. Mussio-Fournier et al.¹⁸³⁹ reported 3 cases of asthma in echinococcus patients, in 2 of them, the asthma disappeared after surgical removal of the echinococcus. A similar case was described by Benhamou.¹⁸⁴⁰

Asthma due to infestation with ascaris (De Besche, Earle¹⁸⁴¹), schistosoma (Mainzer¹⁸⁴²), or *Bothriocephalus latus* (Coniglio¹⁸⁴³), and rhinopathy and conjunctivitis due to oxyuris (Morenas,¹⁸⁴⁴ Gaetz), will be recognized more often when the attention of allergists is turned in this direction.

In this connection, the experimental work of Morenas¹⁸⁴⁵ is of particular interest. He suc-

ceeded in allergizing animals by the intestinal route with extracts of taenia and ascaris. Rocha e Silva¹⁸⁴⁶ elicited reactions in dogs and guinea pigs indistinguishable from anaphylactic shock by means of an intravenous injection of a specially prepared deproteinized extract of *Ascaris lumbricoides* containing glyco-gen like and proteose like substances. Since the animals did not receive a preparatory injection of the extract, the shock was attributed to an endogenous, spontaneously acquired sensitization of allergic nature, due to the presence of parasites in the intestinal tract. Similar effects were produced by hydatid fluid from sheep, calf, and pig, reinjection failing to cause shock (Rocha e Silva and Grana¹⁸⁴⁷).

Occasional cases of urticaria associated with and caused by malaria have been reported, most recently by Mojumdar¹⁸⁴⁸ and Bhownick¹⁸⁴⁹ as well as rare instances of asthma. Antimalarial therapy controlled the symptoms. According to these authors, the liberation of the merozoites in the blood and their subsequent breakdown releases a large amount of foreign substances into the circulation and thus brings about hypersensitization.

¹⁸³⁹ MUSSIO-FOURNIER J. C. SEDANE C. ROCCA F. and BARZANTINI J. C. Arch. méd. chir. d'app. respir. 7: 296, 1932.
¹⁸⁴⁰ BENHAMOU E. THIOUET and CASANOVA J. Paris med. 107: 138, 1938.

¹⁸⁴¹ EARLE K. V. Tr. Roy. Soc. Trop. Med. & Hyg. 37: 451, 1944.

¹⁸⁴² MAINZER F. J. Allergy 10: 349, 1939.

¹⁸⁴³ CONIGLIO C. Giorn. d. clin. med. 4: 266, 1923.

¹⁸⁴⁴ MORENAS L. Lyon med. 145: 403, 1930.

¹⁸⁴⁵ Idem. Arch. d. mal. d'app. digest. 16: 1035, 1926.

¹⁸⁴⁶ ROCHA E SILVA M. Foreign Letters J. A. M. A. 129: 473, 1945.

¹⁸⁴⁷ Idem and GRANA A. Am. J. Physiol. 143: 306, 1943.

¹⁸⁴⁸ MOJUMDAR N. G. Calcutta M. J. 41: 240, 1944.

¹⁸⁴⁹ BHOWMICK S. K. Indian M. Gaz. 8: 48, 1945.

Part Three

SYMPTOMATOLOGY AND THERAPY OF ALLERGIC DISEASES

CHAPTER XX

ANAPHYLACTIC SHOCK

THIS chapter will be devoted to a discussion of the severe symptoms that sometimes appear in human beings after injections of foreign serum, and also occasionally after oral, rectal, or cutaneous administration of other antigens. The less severe anaphylactic clinical syndromes, such as serum sickness and local anaphylaxis (Arthus phenomenon) will not be considered here, since they have been discussed elsewhere. The reader is referred to the section on experimental anaphylaxis for details regarding anaphylactic manifestations in animals, some of which are similar to those seen in human beings, while some are entirely different, owing to the fact that different organs are the shock structures.

A. ETIOLOGY

In view of the fact that literally millions of prophylactic and therapeutic injections of foreign serums have been given—not to mention the countless tests with a multitude of proteins—it is evident that severe anaphylactic shock is by no means a common occurrence. Thus, W. H. Park¹⁸⁰ of the Department of Health of New York City reports that among 30,000 adults treated with antitoxic serum, severe reactions were observed only in 2 instances, and there were no deaths, of 105,000 children receiving diphtheria antitoxin, only two died, the autopsies revealing so-called status lymphaticus.

E. A. Park¹⁸¹ made a compilation of the outcome of 350,000 serum injections. This material revealed an incidence of fatal reactions in 1 out of 50,000 cases, and of alarming symptoms in 1 out of 20,000. In a series of

6,211 patients treated with therapeutic horse serum for various infections Kojis¹⁸² noted a mortality rate of 1 in 1,242, a much greater incidence. In the entire literature from 1894 to 1923, inclusive, Lamson¹⁸³ found mention of only 41 cases of death in anaphylactic shock following injections of protein. Eleven additional instances of this kind were noted by Vaughan and Pipes¹⁸⁴ in the literature for the years from 1924 to 1936. These authors point out, however, that in all probability only a small percentage of all the fatalities have been published by the attending physicians. Moreover, on the occasion of an exhibit on allergic shock at a meeting of the American Medical Association, Vaughan and Pipes interviewed fifty physicians on the subject, about half of them replied that severe shock or death had been observed by them in their own practice, or at least by colleagues personally known to them. Vaughan adds the remark, however, that many of these physicians probably attended the exhibit in the first place because they had had unpleasant experiences of this nature. On the basis of the replies received to a questionnaire, Hinstorff reported that in Germany, in a period of two years, 1,327 physicians observed 147 cases of anaphylaxis resulting from prophylactic antitetanus injections, of which 8 cases were fatal.

However, severe anaphylactic shocks have been observed as a result not only of serum injections, but also of administration of a great variety of protein and other antigens. To mention just a few examples: Baagøe reported anaphylactic death following intracutaneous injection of 0.1 cc. of chicken protein;

¹⁸⁰ PARK, W. H.: Tr. A. Am. Physicians 28, 93, 1913.

¹⁸¹ PARK, E. A.: Am. J. Dis. Child. 19, 46, 1929.

¹⁸² LAMSON, R. W.: J. A. M. A. 82, 1091, 1924.

Cooke, following skin tests with glue, Lamson, with buckwheat, Vaughan and Pipes Lamson, and others, injection of pollen, Wald bott and Ascher, injection of novocain, and a number of authors have reported death following bee and wasp stings. Anaphylaxis is not unknown after injections of tetanus toxoid (see p 361). Even immune globulin has been noted to produce a fatality.¹²⁸¹ An unusual case of sudden death from allergic shock was described by Lund and Hunt.¹²⁸² The subject, later found to have been asthmatic, died within sixteen minutes of the experimental intradermal injection of 0.2 cc. of a solution of guinea pig hemoglobin. Although the deceased had had no known contact with guinea pigs, antibodies specific for some component of guinea pig blood were demonstrated in her serum by means of the Prausnitz-Kuestner reaction.

It would be inaccurate, however, to designate anaphylaxis as a disease resulting exclusively from injections or insect stings. A number of cases of anaphylactic shock with fatal outcome were observed to be due to orally administered antigens, as reported by Finkelstein, Finizio, Salés, Debray, and Verdier, Watson (milk), Halberstadt (buttermilk), von Stark (peas), etc.

Moreover, Black Schaffer¹²⁸⁶ reported five deaths following therapeutic use of sulfonamide compounds, attributed to relatively slow but fatal anaphylactic reactions. The necropsies revealed lesions identical with those observed to have been produced in a few human subjects and many animals by known species-foreign proteins. These findings, along with the knowledge that the sulfonamide compounds may convert homologous (serum or blood cell) proteins into allergens and the fact that characteristic clinical syndromes follow the administration of these drugs, constitute sufficient evidence to justify the concept of the anaphylactic nature of these cases.

Severe but nonfatal manifestations have not infrequently been reported in connection with all manner of prophylactic and therapeutic serums, extracts of pollens, epidermals, and dust, egg white and other food proteins, and also drugs such as quinine and potassium io-

dide. The senior author has observed a severe shock following introduction into the rectum of a papaverine suppository.

There is still a considerable diversity of opinion as to the pathogenesis of anaphylactic shock. A number of authors believe that, like serum sickness, it is invariably due to an antigen-antibody reaction. Others particularly the French authorities, hold that the shock is due primarily to a disturbance of colloidal balance. Further details will be found in Part One.

B SYMPTOMATOLOGY

As the name indicates, anaphylactic shock is characterized by systemic collapse due to severe circulatory disturbances. The clinical picture is striking. During the injection or immediately after it, vomiting and violent colonic spasms appear, causing unbearable abdominal pain and uncontrollable diarrhea. There is an abrupt fall in the blood pressure, accompanied by a drop in temperature (although in occasional instances the temperature will rise). The patient becomes strikingly pale and finally cyanotic. Tachycardia is very commonly observed, thus can be so extreme that the pulse becomes imperceptible, and the heart sounds barely audible. Acute pulmonary emphysema may ensue. The general condition becomes progressively worse, and the patient loses consciousness. Then, unless the proper measures are instantly carried out, death is likely to occur within a few minutes. Fortunately, however, the most severe of these manifestations of anaphylactic shock occur only in exceptional cases.

For didactic reasons—despite the fact that they almost always appear simultaneously—it seems best to consider the clinical symptoms according to their localization, i.e., in the skin, in the gastro intestinal tract, or in the vascular, respiratory, and nervous systems, and to give separate consideration to general manifestations.

Not infrequently the first expressions of anaphylactic shock are intense itching, particularly of the palms, and the appearance at the injection site of a strong urticarial reaction with progressive local edema. These are generally followed by an exanthem covering the entire body, this is usually urticarial, but

¹²⁸² LUND H. and HUNT E. L. Arch. Path. 32: 664 1941

sometimes scarlatiniform. The face and especially the lips and eyelids are often tremendously swollen: this angioneurotic edema and the accompanying intolerable pruritus do not usually persist longer than from seven to eight hours, but they commonly show a tendency to recur over a period of many days. In less severe cases the skin of the face, neck, and anterior chest may assume a rather typical dusky erythematous appearance. The eyes are almost always suffused.

The gastro-intestinal manifestations are not infrequently initiated by nausea followed by vomiting. The colicky pains are often so intense that the patient writhes on his bed in agony, and the diarrhea is so severe that bloody stools are passed. Both the vomiting and the diarrhea usually recur after a symptom-free period of variable duration.

The symptoms related to the vascular and respiratory systems are especially alarming. The pulse becomes weak and rapid, the blood pressure drops; dyspnea sets in at the same time, and there is often a severe attack of asthma.

Among the nervous symptoms, convulsions deserve special mention.

The general condition is invariably bad. The patient is in a state of extreme apprehension. He suffers from a sensation of heavy pressure in the head, accompanied by ringing in the ears, dizziness, and sometimes palpitation. The feeling of general prostration often persists for days.

Particularly dangerous are those cases in which the symptoms appear with lightning speed. Not infrequently, however, the manifestations do not develop immediately, but only after many hours—especially when the injection has been given intramuscularly rather than intravenously. Thus Gammelgaard¹⁸⁴ reported a patient whose first symptoms appeared four days after an intramuscular injection of tetanus antitoxin and whose death did not occur until the seventh day. Waldbott calls attention to the fact that anaphylactic shock can take place without the occurrence of an urticarial reaction or an asthmatic attack. This observation has been confirmed by Vaughan.

Necropsies performed by Vance and Strassmann¹⁸⁵ on seven persons who died from injections of foreign protein revealed pronounced inflation of the lungs and signs of asphyxia due to bronchial spasm. Abnormal numbers of eosinophilic leucocytes were present in the bronchial walls. Cerebral edema and laryngeal edema were each found in two cases, and were attributed to increased capillary dilatation. In the five cases studied by Black-Schaffer¹⁸⁶ the basic lesion was a necrotizing fibrinoid arteritis of the smaller vessels with a cellular exudate of monocytic composition. The reticulo-endothelial system was hyperplastic.

C. THERAPY

For a discussion of the prevention of anaphylactic shock, the reader is referred to the section on foreign serums.

When an anaphylactic reaction threatens to develop, the patient should be made to lie down at once, and a tourniquet should immediately be applied above the site of injection. Epinephrine (0.5 cc. of a 1:1,000 solution) is first injected subcutaneously into the opposite arm, and an equal dose into the injection site. If possible the tourniquet is then replaced by a sphygmomanometer, for this offers the advantage of permitting control of the pressure in such a way that the venous return is completely stopped, but not the arterial supply. In the beginning, the pressure is released for only a few seconds at a time; later it is released for several minutes. It is advisable to determine the blood pressure from time to time. An elevated blood pressure shows that the patient is under the influence of adrenalin; on the other hand, subnormal pressure despite the administration of epinephrine is an indication that the anaphylactic shock is not controlled. In the latter case, the patient is given another injection of epinephrine. It is often necessary to wait two or three hours before removing the pressure cuff altogether. If cyanosis or numbness of the hand appear, the tourniquet is released for a short time. Local instillation of vasoconstrictors (2 to 3 per cent epinephrine sulfate solution, 1:1000 epinephrine hydrochloride) will relieve the

¹⁸⁴ GAMMELGAARD, A. *Acta path. et microbiol. Scandinav.* 19: 1, 1942.

¹⁸⁵ VANCE, B. M., and STRASSMANN, G. *Arch. Path.* 34: 849, 1942.

nasal symptoms, and ice or cold water may be applied to pruritic areas.

In especially severe cases, epinephrine must be injected intravenously, preferably in the form of a slow infusion of 1 cc of epinephrine in 250 cc of warm physiologic salt solution. If this is not available, 0.2 cc of epinephrine diluted with 10 cc of saline solution or the patient's withdrawn blood may be given very slowly intravenously by syringe. Asthmatic symptoms can be almost always controlled by intravenous aminophylline. In some cases it is also advisable to administer a cardiac

stimulant such as coramine. Further a mild degree of anesthesia (ether) may be well worth trying.

If laboratory examination of the blood reveals hemoconcentration 2000 cc of physiologic salt solution should be given intravenously over a period of two hours (Blotner^{18, 19}). For this purpose human plasma may be injected intravenously, as successfully employed by Raynolds.^{19, 20}

¹⁸ *BLOTNER H. J. A. M. A 118: 219, 1942.

¹⁹ **RAYNOLDS A. H. J. Allergy 14: 493, 1943.

CHAPTER XXI

ALLERGIC DISEASES OF THE UPPER RESPIRATORY TRACT

A. ALLERGIC AND PATHERGIC RHINOPATHY (VASOMOTOR RHINITIS)

THE term allergic rhinopathy designates a disease picture characterized by paroxysmal attacks of sneezing, nasal obstruction, and serous rhinorrhea, usually of short duration, not accompanied by any of the constitutional symptoms ordinarily found in infectious rhinitis, and generally not confined to any particular season. The latter point serves as the main criterion for differentiation between this condition and hay fever. Because of its greater frequency, hay fever, although likewise an allergic rhinopathy, has been arbitrarily excluded from this group for separate consideration. It should be added, however, that under certain circumstances allergic rhinopathy may also be strictly seasonal as, for example, when the patient suffers his attacks only after ingestion of some seasonal fruit or vegetable. It is also apparent that in regions where the pollens are present in the air all through the year, as in southern California (Smith et al.¹⁸⁴), perennial rhinopathy, as well as other forms of respiratory allergy such as sinusitis and bronchitis, may represent an unrecognized or hidden pollinosis.

It is difficult to estimate the incidence of allergic rhinopathy in the general population, but Feinberg¹⁸¹ believes that it occurs in 0.5 to 3.0 per cent. Since many patients do not seek treatment, the actual percentage may be even higher.

1. TERMINOLOGY

A considerable number of terms have been suggested to designate this syndrome: vasomotor rhinitis, perennial (nonseasonal) allergic rhinitis, paroxysmal rhinitis, nervous rhinitis, hyperesthetic rhinitis, extrinsic and intrinsic rhinitis, allergic coryza, spasmodic coryza, atopic coryza, contact allergic coryza, paroxysmal rhinorrhea, perennial hay fever, hydro-

nasals, and allergic rhinopathy. Most of the proposed designations must be rejected a priori for they are just as vague as "vasomotor rhinitis" (e.g., nervous rhinitis, hyperesthetic rhinitis, spasmodic coryza, paroxysmal rhinitis). Other terms (e.g., contact allergic coryza, perennial allergic rhinitis) are appropriate for only a small group of cases. At first glance, Rackemann's suggestion of dividing the cases as extrinsic and intrinsic rhinitis, on the basis of mode of causation, seems satisfactory. The extrinsic factors of causation include chiefly those substances that act by way of inhalation (house dust, animal danders, orris root) the intrinsic factors comprise (1) substances that produce their effects by ingestion (e.g., foods and drugs) and (2) bacteria. On more careful consideration, however, it becomes evident that, under different etiologic conditions, foods such as wheat flour and other cereals, the odors of fish, egg, or asparagus, as well as drugs, are capable of producing extrinsic rhinitis by inhalation.

In our opinion, the correct general designation would be rhinopathy, under the widely accepted usage of the suffix "-pathy." In contrast with the term rhinitis, rhinopathy does not suggest an inflammatory condition. Subclassification could be undertaken along the lines of the authors' proposed division of the phenomena of hypersensitiveness as allergic and pathergic, as follows: when the causation is specific-allergic, the condition may be referred to as an allergic rhinopathy, on the other hand, when the causation is a nonallergic hypersensitiveness, the disorder might be called pathergic rhinopathy. The same subdivisions are employed in the discussion of bronchial asthma.

2. ETIOLOGY AND PATHOGENESIS

In each case, the basic question, and a consideration of decisive importance in determining the therapy, is whether the disease is of allergic or pathergic origin. It must be remembered that not all patients who sneeze and have intumescent membranes are necessarily suffering from an allergic condition. Further-

¹⁸⁴ SMITH, H. D., GOODWILL, V., and WEBB, M. E. *California & West. Med.* 58: 275, 1943

more, the fact that the patient is allergic does not mean that his rhinopathy must be due to this condition. In an appreciable percentage of cases, there is hypersensitiveness of the nasal mucosa that does not depend upon an antigen-antibody reaction. Cases of this kind include those in which paroxysmal sneezing, with subsequent swelling of the nasal mucosa, follows a sudden change in temperature or exposure to cold wind, hot air (Duke¹⁸⁵⁷), looking up into strong sunlight (Freund,¹⁸⁵⁹ Duke¹⁸⁶⁰), or particularly such atmospheric factors as abrupt fluctuations in humidity and barometric pressure (before storms, change of altitude), or exposure to drafts. Furthermore, smoke (tobacco, coal, gas, oil, vapors of burning sulfur), as well as the odors of various perfumes, and soap powder have frequently been found to act as eliciting agents. Less commonly formalin, benzene, naphtha, printing ink, and other chemicals are responsible for the symptoms. Furthermore, one must always remember the potential causative rôle of mechanical influences, such as those due to sharp pointed particles—e.g., "hairs" of royal palms, plane trees (Benjamins¹⁸⁶¹), or barley dust.

Aside from these nonspecific, exogenous factors there are quite a few patients in whom psychosomatic influences play a most important part in eliciting paroxysmal coryza. Emotional upsets, quarrels, sexual conflicts, fatigue, overwork—these are only a few of the psychic factors on which these patients will place the responsibility for their nasal attacks, though they rarely make such an admission until they have been carefully interviewed and until the physician has won their confidence. A case observed by Lieschke is characteristic. A girl suffering from rhinopathy was relieved of her symptoms when she was betrothed but suffered a relapse when the engagement was broken a few months later. The writers have observed a number of cases in which psychic factors were the principal cause of rhinopathy.

Aside from conditions based on pathergic hypersensitiveness of the nose, there are, of course, numerous instances of rhinopathy of

allergic origin—among which hay fever cases will naturally not be considered here.

The identification of the causal allergen is then to be undertaken by the methods described on page 156. It might be well to stress once again that skin tests should not be the only method of study; that, if possible, nasal testing should be instituted as well, and that exposure and elimination experiments are certainly the most reliable.

Nevertheless, Vallery Radot¹⁸⁶² reported that among 188 cases of paroxysmal coryza, he was able to determine the identity of the causal agent by skin tests in 107 instances. A positive skin test must, of course, be regarded as specific if it is accompanied by a focal reaction in the form of an acute and sudden "cold," as observed by the present writers following an intracutaneous injection of 1:500,000 ursol solution.

Concomitant presence of other allergic diseases, particularly hay fever, suggests the possibility of an allergic origin of the patient's rhinopathy, as does a strong family history of allergy.

As for the causative agents, we shall select, for brief mention—from the very extensive literature that has appeared on the subject during the past few years—only a few of the most commonly encountered allergens.

Above all, one must consider the exogenous allergens in the patient's home, this can best be done by means of the day and night tests (see p. 194). This group of allergens comprises house dust first and foremost, then mattress stuffing (horsehair, cotton linters, kapok), upholstery filling, feather pillows and feather quilts (goose, duck, chicken feathers), woolen blankets, rugs, pyrethrum animal skins, and library dust. Other important exogenous allergens include fungi, particularly *Alternaria* and *Hormodendron* (Waldrott et al.,¹⁸⁶³ Morrow et al.,¹⁸⁶⁴ and others), smuts and rusts, butterfly scales, sandflies, and even the house fly (Jameson¹⁹⁰⁸), articles of clothing, as wool and silk underwear, dyed and undyed furs, dyed blouses, human hair and dandruff, animal

¹⁸⁵⁹ VALLERY RADOT, P. BEAUMOUTIER, P. and JUSTIN BESANCON. L. Presse méd. 36: 625, 1928.

¹⁸⁶⁰ WANDROFF, G. L., BLAIR, K. E. and ACKLEY, A. B. J. Lab. & Clin. Med. 26: 1593, 1941.

¹⁸⁶¹ MORROW, M. B., LOWE, E. P. and PRINCE, H. E. J. Allergy 13: 215, 1942.

¹⁸⁵⁸ FREUND, L. Strahlentherapie 21: 518, 1926.

¹⁸⁵⁹ DUKE, W. W. Radiology 4: 279, 1925.

¹⁸⁶¹ BENJAMINS, C. Geneesk. tijdschr. v. Nederl. Ind. 72: 1016, 1932.

emanations and animal hair and dander (horse, dog, cat, rabbit), volatile oils (acacia, hnden, jasmine, rose, lilac, lemon); occupational dusts, such as those of flour, cottonseed, castor bean, tobacco, wood, leather, drugs, chemicals, flour-improving preparations, upholstering and packing materials such as the fibers of Spanish moss (Dean⁷⁷³); orris root in powder, soaps, shampoo preparations, cosmetic creams, bath salts, perfumes, etc.

Second, one must consider the possibility of causation by some food. We are indebted to Sticker¹⁸⁶¹ for one of the first observations in this connection. He noticed that a patient regularly suffered from severe attacks of sneezing, extraordinarily copious watery nasal discharge, and lacrimation, after ingestion of strawberries, furthermore, this patient's uncle presented the same symptoms after ingestion of cherries, while fresh or dried sorrel elicited similar manifestations in the latter's cousin. Muenich reported the case of a woman who invariably was afflicted with acute rhinitis following ingestion of tomatoes. Joltrain¹⁸⁶⁴ observed urticaria and rhinopathy following the drinking of beer. Gould and Pyle, as well as Klewitz, described sneezing after ingestion of chocolate. Similar observations have been reported by Ruskin,¹⁸⁶⁵ Dutheiliet¹⁸⁶⁶ (meat, fish), Urbach and Fasal¹⁸⁶⁸ (eggs), Harley¹⁸⁶⁷ (wheat), Vaughan,¹⁸⁶⁹ Adelsberger and Munter¹⁸⁶⁹ (vegetables, fruit), Salén¹⁸⁶³ (Brazil nuts), Nadoleczny (spices), and others. Chiefly by skin tests and partly by means of diets, Eyer mann,¹⁸⁶⁹ Rowe,⁷¹⁰ and others succeeded in identifying the following foods as the commonest causal agents in nasal allergy: wheat, egg, milk, chocolate, potato, bean, pea, salmon, tomato, onion, beef, rye, grapefruit, pear, peach, and pineapple (in this order of frequency in their material). Of the 95 cases studied by Eyer mann, 8 were monovalent, with hypersensitiveness to only one food, 87 of the patients, on the other hand, were hypersensitive to a number of items. Needless to say, the authors mentioned frequently found

that the food in question was not the sole cause of the allergic symptoms, but was often active only in combination with animal emanations, dust, or other allergens. Among 441 cases, Balyeat¹⁸⁷⁰ found that foods were the principal allergens in 4.9 per cent, and the secondary cause in 24 per cent. Gelfand's¹⁸⁷¹ figures are about the same.

Not to be confused with these instances are others in which the mere odor of a certain food is sufficient to elicit either an urge to sneeze or actual attacks of sneezing. The writers were able to ascertain that the odors of the following foods could act as allergens: fish, milk, egg, asparagus, coffee, and lemon, as well as the odor of frying food and of roast hare.

In the third place, drugs administered by mouth, as well as others given parenterally, are occasionally the cause of rhinopathy: quinine (Dawson and Newman¹⁸⁷²), amidopyrine (Bayer), aspirin (Vallery-Radot and Heilmann¹⁸⁷³), salicylic acid by injection (Griebel¹⁸⁷⁴), and atropine in eye drops, although the eye itself presented no symptoms (van der Hoeve).

In the fourth place, some cases may be assumed to be based on a bacterial allergy. It is true that rhinopathy may result when a chronic infection increases the reactivity of the neurovasomotor and exudative mechanisms of the nasal mucosa to multiple nonspecific irritation, or when an infection predisposes to hypersensitiveness to a specific allergen. Nevertheless, the results of investigations by Lakos¹⁸⁷⁵ and the senior author point to the fact that in many cases a genuine bacterial allergy may be assumed to be the cause of rhinopathy. The writers are inclined to make this diagnosis when the foci of infection are in the sinuses, the middle ear, or the tonsils, and when cure of these by means of operation, sulfonamides, penicillin, or other therapy brings about a cessation of the nasal symptoms. Further confirmation of this diagnosis is found in cases in which autogenous vaccines from these foci of infection elicit not only a strongly positive

¹⁸⁶⁵ RUSKIN, S. L. *Laryngoscope* 40: 751, 1930

¹⁸⁶⁶ DUTHEILLET DE LAMOTHE, G. *Ann. d. mal. de l'oreille, du larynx* 41: 257, 1922

¹⁸⁶⁷ HARLEY, D.: in Kallós, P. (ed.) *Fortschritte der Allergologie*, Basel, Karger, 1939, p. 137

¹⁸⁶⁸ SALÉN, E. *Acta med. Scandinav.* 78: 197, 1932

¹⁸⁶⁹ EYERMAN, C. H. *J. Allergy* 1: 350, 1930; *South. M. J.* 31: 710, 1938

¹⁸⁷⁰ BALEYAT, R. M. *Allergic Diseases*. Philadelphia: Davis, 1930

¹⁸⁷¹ GELFAND, H. A. *Arch. Otolaryng.* 37: 1, 1943

¹⁸⁷² DAWSON, W. T., and NEWMAN, S. P. *J. A. M. A.* 97: 930, 1931

¹⁸⁷³ VALLERY-RADOT, P., and HEILMANN, V. *Hypersensibilités spécifiques dans les affections cutanées*. Paris: Masson, 1930.

¹⁸⁷⁴ GRIEBEL, C. R. *Klin. Wchschr.* 17: 164, 1938

¹⁸⁷⁵ LAKOS, Z. T. *Acta oto-laryng.* 17: 400, 1932

skin reaction but also a nasal (focal) response in the form of an attack of sneezing and nasal obstruction. Shambaugh⁸⁶ states that 90 per cent of chronic nasal infections can be shown to have an underlying allergic factor.

A question now being studied by the writers is whether *Bacillus proteus* which is occasionally found in nasal secretions and which when injected intracutaneously evokes severe focal and systemic manifestations—in some patients even in a dilution as high as 1:1,000,000,000—is justifiably to be regarded as an allergen.

At this point attention should be called to the splendid work of Jacobson and Dick,⁸⁷ on the normal and abnormal bacterial flora of the nose. These authors found that the normal nasal flora consists chiefly of *Staphylococcus albus* and diphtheroid bacilli with *Staph aureus* and *Micrococcus catarrhalis* occurring less frequently. The presence of streptococci, *B. mucosus*, Pfeiffer bacilli and diphtheria bacilli indicates disease of the nasal mucosa or sinus disease or both.

Lastly, it may be said that it is likely that endogenous allergens play a greater role in the pathogenesis of rhinopathy than is generally supposed today. An interesting and pertinent case is reported by Riebel.⁸⁸ Regularly on the day prior to the onset of menstruation the patient suffered attacks of sneezing, nasal obstruction, chills, fever of about 101 F and prostration. These manifestations disappeared completely after three or four days. When the patient was given injections of 1 cc of an aqueous solution of folliculin during the intermenstruum the same symptoms appeared but in a milder form than during the menstrual period. A course of thirteen injections within two months resulted in a complete cure. (Such cases should not be confused with those commonly seen in which the rhinorrhea tends to be exacerbated immediately before menstruation probably owing to the increased nervous tension at that time.) Adlersberg and Forschner^{87a} and Koerbel and

Wiethe^{87b} have described similar observations in relation to menopausal women; the nasal manifestations were ascribed to endocrine disturbances and were found to be satisfactorily controlled by estrogenic therapy. Laub⁸⁹ observed that rhinopathy often develops at the time of the climacteric in men as well as in women. These cases may be improved by testicular or ovarian extract. In a group of 1900 obstetrical patients Mohun⁹⁰ found 20 who manifested a definite increase of rhinopathy and associated conditions during pregnancy. Eight of them had nasal obstruction or congestion only while gravid and reported a similar condition during one or more previous pregnancies. He believes that the manifestations parallel the amount of estrogen produced. Typically the symptoms disappear spontaneously within one to seven days after delivery.

Mention should also be made in this connection of those instances in which there is a definite relationship between constipation and rhinopathy and which can be successfully managed by proper treatment of the constipation (Adlersberg and Forschner^{187a}, Urbach⁹¹). Furthermore the not so very rarely observed cases of rhinopathy due to oxuriasis (Goetz Hedderich) may likewise belong to this category.

At this point it may be of interest to report on a series of 74 cases of rhinopathy in which there was no history nor any evidence of asthma at the time of examination. Owing to the unusual nature of the material the results differ to some extent from the figures usually given since the latter comprise chiefly cases with both rhinopathy and asthma. The reader is referred to the section on asthma (p. 600) for an analysis of 145 cases of rhinopathy in patients who have or have had asthma.

As Table 40 shows 60 of the cases (81 per cent) belong to the pathergic groups—that is to say these cases are caused by a variety of nonspecific factors. We may subdivide them according to the primary noxae as cases of

* SHAMBAUGH G. E. Jr. Ann. Oto. Rhin. & Laryng. 34: 43, 1915.

* JACOBSON L. O. and DICK G. F. J. A. M. A. 117: 2222, 1914.

* ADLERSBERG D. and FORSCHNER L. Monatsh. f. Ohrenh. 66: 397, 1932.

** KOERBEL V. and WIETHE C. b.d. 70: 603, 1936.

= LAUB G. R. Laryngoscope 50: 19, 1941.

** MOHUN M. Arch. Otolaryng. 37: 699, 1943.

** URBACH E. Monatsber. f. Ohrenh. 66: 160, 1932.

rhinopathy on the basis of infection, of irritation, and of psychic influences, and those that once were specific-allergic but became non-specific in the course of time. Of the remaining 20 cases, 3 were due to endocrine and 3 to intestinal disturbances, and 14 were of specific allergic origin.

Allergic and pathergic rhinopathy may occur at any age, but it is most commonly observed in the second and third decades of life. The writers are of the opinion that in the last few years this disease has shown a tendency to appear earlier in life, and they now

band, male cases have been found to outnumber female in the incidence in the first decade of life (Winkenwerder and Gay^{135a}).

Heredity plays a somewhat less important rôle in rhinopathy than in asthma. Environmental factors are of far greater importance, as can be seen by the prevalence of rhinopathy in bakers, millers, and housewives.

Intranasal abnormalities, such as septal deviations, spurs, or hypertrophied turbinates, are often accused of being the cause of rhinopathy, and patients are urged to have these removed. However, in the opinion of the majority of authorities, while these conditions may aggravate the rhinopathy during the actual attacks, they are not etiologically responsible for it. Therefore, surgical intervention is indicated only in those rare cases in which a deviated septum or hypertrophied turbinate seriously interferes with the free passage of air.

Lastly, mention must be made of the influence of a long-lasting rhinopathy on the patient's general condition. This disease is generally regarded by physicians as nothing more than a minor disturbance. And this viewpoint is warranted so long as the symptoms are mild and transitory, but when they become severe and persistent, the patients suffer appreciably, and the difficulty experienced in maintaining an adequate respiratory volume often brings on serious mental depression. Moreover, when one also takes into consideration the numerous complications (acute or chronic sinusitis, as well as asthma) that, when present, seriously interfere with treatment, it becomes obvious that everything possible must be done to recognize and to combat the disease and its causes at the outset. Among the conditions frequently associated with perennial allergy of the nose and paranasal sinuses Hansel^{135b} mentions "involvement of the external ear, eustachian tube, middle ear, cochlea and labyrinth, resulting in deafness, tinnitus, and dizziness, recurring swellings of the parotid and submaxillary glands, involvement of the larynx and esophagus; allergy of the eye; and allergic headache," as

TABLE 40—Classification of 74 Cases of Rhinopathy according to Pathogenesis

Type of Rhinopathy	Pathogenic Basis	No. of Cases	Percentage
Pathergic	infection	30	40.5
Pathergic	irritation	15	20.3
Pathergic	psychic disturbances	4	5.4
Pathergic	previous specific-allergic rhinopathy	5	6.7
Pathergic	endocrinopathy	3	4.0
Pathergic	functional intestinal disorders	3	4.0
Allergic	exogenous allergens	14	19.0

see many children and even infants with rhinopathy. It may be of interest to add that the symptoms in early childhood are due, in the main, to food allergy, especially reaction to milk and to wheat. Very frequently the erroneous diagnosis of recurrent colds is made in the case of such children. But it should also be borne in mind that this condition may first manifest itself late in life, even during the seventh decade.

Women are more prone to have rhinopathy than are men. Huber and Harsh^{135c} reported that female patients constituted 80 per cent of their material; Rackemann²⁹ reported 73 per cent, and Urbach¹³⁵ 54 per cent. Similar observations were made by Clarke and Rogers^{135d} and by Griebel.^{137d} This higher incidence among women may be attributed to the fact that they are more likely to be psychically labile than are men. On the other

^{135c} HUBER, H. L., and HARSH, G. F. *J. Allergy* 5: 432, 1934.

^{135d} CLARKE, J. A., JR., and ROGERS, H. L. *Arch. Otolaryng.* 25: 124, 1937.

^{135a} WINKENWERDER, W. L., and GAY, L. N. *Bull. Johns Hopkins Hosp.* 41: 90, 1927.

^{135b} HANSEL, F. K. 1943 Regional Instructional Course, American College of Allergists.

well as such manifestations as allergic bronchitis Craft¹⁵⁵ even describes facial neuralgia as an atypical complication of nasal allergy

3 PATHOLOGY

Grossly the nasal mucosa may present any of the following appearances depending on the stage and duration of the process normal slightly pale markedly pale or edematous bluish grayish or red Hansel¹⁵⁴ points out that there is no justification for distinguishing an allergic from a nonallergic rhinitis on the basis of pale or red appearance of the mucosa Nasal polyps are however, usually present in cases presenting a pale mucosa

Polyps are smooth pedunculated growths prolapsing from the mucous membrane, they result from marked local edema, and originate from the loose structure of the stroma of the tunica propria They present distended spaces filled with serum plasma cells mononuclear lymphoid and above all eosinophile cells If they persist for any length of time, some fibrosis may result Polyps are most commonly observed and most pronounced on the anterior tips and lower margins of the middle turbinates It is here that the maximal contact with the allergen takes place Furthermore edema and polyposis very frequently occur in the sinuses sometimes even completely filling them The antra and ethmoids are most commonly involved

As Hansel¹⁵⁵ has shown in his fundamental experimental work the histopathologic changes that occur in the nose and in the paranasal sinuses in patients with allergic rhinopathy are in principle similar to those that occur in the bronchial mucosa in allergic asthma At first one can observe edema and a definite eosinophilic infiltration of the epithelial and subepithelial layers In the more advanced stages there are thickening hyperplasia and polypoid degeneration of the epithelial layer, edema eosinophilic as well as mononuclear infiltration of the subepithelial layer hypertrophy and hypersecretory activity of the mucous glands dilatation of the blood vessels and proliferation of the connective tissue The process may also extend to the bones

where partially hypertrophic and partially atrophic changes make their appearance The perosteal layer shows round cell infiltration and connective tissue proliferation Lastly there is the formation of polyps in the nose and sinuses When a secondary infection sets in the eosinophilic leucocytes in the tissues are replaced by neutrophilic leucocytes

4 SYMPTOMATOLOGY

The course of allergic rhinopathy may generally be divided into four types The first comprises those cases in which secretory disturbances occur only during attacks Such a condition—sometimes called *hydrorrhoea nasalis*—is characterized by a thin watery clear secretion that contains very little mucus However when the nasal discharge continues for several days the secretion may tend to become thicker in consistency since more mucin from the mucous glands becomes mixed with it The quantities of secretion produced in the course of an attack of this kind are sometimes amazingly great often requiring the use of many handkerchiefs The patients sometimes describe this condition by saying It runs like a spigot

In the second and far more commonly encountered type the watery nasal discharge is associated with symptoms of intense irritation in the form of nasal tickling and paroxysms of sneezing followed by nasal obstruction resulting from the marked swelling of the turbinates Attacks of sneezing may range from three or four separate sneezes to as many as ten and even twenty or more however these are rarely as strong or as exhausting as in hay fever But the nasal obstruction is at least as annoying to the patient as is the paroxysm of sneezing The obstruction often involves only one side and may be of relatively brief duration In other cases both sides may be blocked simultaneously or alternately first one side and then the other and this may persist for hours and sometimes even for a whole day and night The degree of the obstruction may vary considerably at different times of the day and night depending upon the causal factors It is usually most pronounced in the early morning hours but it is also marked during the night The congested condition of the nose is probably not so very much—and

¹⁵⁵ CRAFT K. L. *J. Intern. Med.* A 37: 180 1944

¹⁵⁴ HANSEL F. K. *J. Allergy* 1: 43 1929

surely not entirely—the result of an inflammatory swelling, but is due rather to a sudden engorgement of the turbinates, which can disappear as quickly as it came. Occasionally, there are also lacrimation and distressing tickling and dryness in the nasopharynx, along with coughing.

The third type is characterized by one or all of the following symptoms: headaches (due to swelling of the mucous membranes of the sinuses), mental depression, lassitude, and constitutional manifestations.

Naturally, there are also transitional forms between these three groups.

Fourth, it is necessary to recognize the atypical and subclinical types of nasal allergy. According to Hansel,¹⁴³² they are characterized symptomatically by stuffiness of the nose, associated with little if any sneezing and practically no discharge except for a thick sticky post-nasal drip. Eosinophilia in these postnasal secretions is usually not marked, but is sufficient to be of diagnostic significance. These low-grade or subclinical nasal symptoms are frequently associated with obstruction of the eustachian tube, swelling of the soft palate, involvement of the parotid gland, and conjunctivitis. The nasal mucosa may be normal in appearance, slightly red, or slightly pale or boggy. Most of these cases are caused by inhalants, particularly house dust.

The connection between rhinopathy and bronchial asthma merits special consideration here. Rackemann²⁰ reported that of 257 patients with allergic rhinitis, 16 per cent had asthma; Winkenwerder and Gay¹⁸³⁸ found this condition in 25 per cent of 198 cases. On the other hand, Rackemann¹⁸³⁹ diagnosed allergic rhinitis in 27 per cent among more than 1,000 asthmatics, and Urbach and Gottlieb¹⁸³¹ in 38 per cent among 379 asthma patients. In our material the percentage was highest among the cases of specific-allergic asthma (about 47 per cent), while the average incidence among the cases of pathergic asthma was 37 per cent. It was found that when the rhinopathy appeared at about the same time as the

asthma, both conditions were brought on by the same causal agent or agents, and that when the nasal condition appeared long before or after the asthma, the diseases were attributable to different agents (for further details, see the discussion of asthma, p. 600). Kern and Schenck¹⁸³² determined the incidence of nasal polyps (a sign of rhinopathy) in asthmatics to be 30 per cent. From these figures it is readily seen that rhinopathy frequently precedes or accompanies bronchial asthma. Occasionally, the patient suffers asthma in childhood and from rhinopathy in adult life, or vice versa.

Allergic as well as pathergic rhinopathy very frequently leads to involvement of the sinuses, causing edematous swelling, inflammatory-infectious hyperplasia, or polyps. These conditions will be discussed in the section on sinusitis.

Furthermore, mention should be made here of the deformities of the facial bones that, as Duke¹⁸³³ has pointed out, result from long-continued allergic rhinopathy in childhood. These consist of a depression and flattening of the nasal bone, probably attributable to inadequate development of the sphenoids and antra.

Lastly, there is Fugisawa's statement to the effect that patients with allergic rhinopathy often present a blood eosinophil count of from 15 to 20 per cent during their attacks. According to Griebel,¹⁸⁷⁴ it is preferable to make the examination shortly after the attack. In subacute or chronic cases, the blood picture is dominated by lymphocytosis, eosinophils being either absent, or present in small numbers only. However, according to Griebel, when a protein-free splenic extract is injected, these cases present definite eosinophilia, while normal individuals show no change. (For a discussion of eosinophilia in the nasal secretion, see below.)

The clinical course depends on whether the allergic or pathergic causation can be found and eliminated, or whether the patient can be specifically or nonspecifically hyposensitized. If this goal is not attained, sinusitis and/or asthma may ensue and ultimately replace the former condition.

¹⁴³² Idem Arch Otolaryng 34 1152, 1941

¹⁸³⁰ RACKEMANN, F. M., and TOBES, H. G. ibid 9 612, 1929

¹⁸³¹ URBACH, E., and GOTTLIEB, F. M. Arch Pediat 59 382, 1912

¹⁸³² KERN, R. A., and SCHENCK, H. P. J. Allergy 4, 455, 1933

¹⁸³³ DUKE, W. W. Arch Otolaryng 12, 493, 1930

5 DIFFERENTIAL AND ETIOLOGIC DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The principal characteristics of allergic and pathergic rhinopathy including those that distinguish it from hay fever, were described in some detail at the beginning of this section. Here we shall chiefly consider the problem of differentiating rhinopathy from the "common cold" due to virus and bacterial infection of the nasal mucous membrane, since the latter condition is most commonly confused with it. It must be mentioned, however, that the layman employs the term "cold" for any kind of acute coryza, just as he generally calls all chronic nasal inflammations "sinusitis."

TABLE 41—Major Types of Cytologic Findings of Nasal Secretions

Type	Eosinophils	Neutrophils	Organisms	Epithelial Cells
Allergic	++++	0	0	+ or 0
Infectious	0	+++	+++	+
Bacterial Allergy or Secondary Infection Superimposed on an Allergic Response	++	+++	+++	+

When the symptoms set in suddenly with paroxysmal sneezing followed by profuse watery rhinorrhea and nasal obstruction, usually of short duration and when these symptoms are not accompanied by any systemic manifestations, it is highly probable that the case is one of allergic coryza. But if, on the other hand, the onset is gradual, with slight sneezing, if there is irritation in the nasopharynx, with a thick and mucoid nasal discharge that subsides only after two or three days or becomes grossly purulent, and if there is general malaise and even a febrile reaction—then the condition is more likely to be a true rhinitis of infectious origin, or a "common cold."

Moreover, as Hansel¹⁸⁹⁴ has pointed out, one of the most decisive factors in the differential

diagnosis is the cytologic character of the nasal smear. In allergic coryza, numerous eosinophils are present, in the "common cold" one observes polymorphonuclear neutrophils as the predominant cells, while the eosinophils are few in number or totally absent. The smears should also be examined for the presence of microorganisms and epithelial cells. The typical cytologic responses are shown in Table 41, from Mansmann¹⁸⁹⁵.

In view of the importance of this method of differential diagnosis, a detailed description of the use of the new polychrome stain developed by Hansel¹⁸⁹⁶ will be given here. The method is simple, rapid, and reliable, and can also be applied to bronchial secretions. (If this stain is not available, a combined Wright-Giemsa technic, as for malaria smears, can be successfully employed.)

TECHNIC OF STAINING NASAL AND BRONCHIAL SECRETIONS (HANSEL¹⁸⁹⁶)

- 1 Collect secretion by having patient blow nose on waxed paper.
- 2 Transfer secretion to slide—tease out with tooth pick so as to avoid thick masses. Make two or three smears if there is enough material.
- 3 Dry smears in air or gently over flame.
- 4 Mark across slide next to label with paraffin stick to prevent overflow.
- 5 Cover completely with polychrome stain and allow to stand thirty to forty five seconds giving the longer period to thick or milky smears.
- 6 Add distilled water to take up stain as in Wright's technic and allow to stand about thirty seconds. For best results neutralize the distilled water by adding 1 drop of 1 per cent potassium carbonate to each 30 cc.
- 7 Pour off stain and flood slide with distilled water to remove excess stain.
- 8 Flood slide with 95 per cent ethyl alcohol. Drain off and dry slide over flame.
- 9 If the blue color is too intense flood slide with 95 per cent ethyl alcohol to which 1 drop of 1 per cent hydrochloric acid has been added to 30 cc. The amount of blue color removed depends on the length of time the acid alcohol is allowed to remain on the slide.
- 10 Pour off acid alcohol and then flood with plain 95 per cent ethyl alcohol again.
- 11 Always examine the stained smear under the microscope before using the acid alcohol solution. The acid treatment intensifies the red in the eosinophiles by removing overlying blue. Too much acid may take the blue out of the neutrophils and give them a pink color. If the neutrophils are pink upon the first

¹⁸⁹⁴ HANSEL F. K. J. Allergy 10: 251 1939

¹⁸⁹⁵ MANSMANN J. A. Ann Allergy 3: 191 1945

¹⁸⁹⁶ HANSEL F. K. cited by Mansmann¹⁸⁹⁵

examination, stain another specimen and allow about fifteen to twenty seconds longer for stain to act before adding the water.

12 In the examination of smears, the magnification must be 125 to 150. Using a 10 X objective, the eye piece, therefore, should be 12.5 or 15 X. Use a moderately strong clear light.

The eosinophils are easily recognized as larger than the neutrophils, and contain large acidophilic granules stained a brilliant orange red. Many will be ruptured and the eosinophilic granules loosely scattered. The nuclei are usually bilobed and stain blue. The neutrophils and epithelial cells will contain a deep blue nucleus and a lighter blue cytoplasm. Mucus will stain blue.

To secure an appropriate nasal specimen, it is best to have the patient use a piece of ordinary crumpled cellophane in lieu of a handkerchief, and to make use of spontaneous discharges only. The specimen will remain sufficiently moist for two or three hours if the "handkerchief" is twisted and sealed in an ointment jar. It is best to examine the discharge of each nostril separately, since occasionally only one side discloses evidence of an infection. In children too young to blow their noses properly, the secretion can be obtained by swabbing with a cotton applicator.

It is often necessary, however, to make repeated cytologic studies over a long period of time. For it not infrequently happens that one does not observe any eosinophile cells in the first examination, either because the nasal discharge is so profuse that it does not contain any cells, or because the examination is made at the very beginning of a nasal allergy. Moreover, according to Hansel, there may also be a great increase in the number of eosinophils in a common acute coryza, however, these cells disappear when the acute symptoms subside. In addition, a patient with allergic rhinopathy may at times acquire an infectious cold. In cases of this kind, there is a change in the character of the nasal discharge, which then becomes thick, viscid, and yellowish. Simultaneously, numerous neutrophils make their appearance, while only isolated eosinophils can be observed. The cytologic picture soon changes, however, when the infection disappears. Not infrequently a large number of both types of cells may be present at the same time; this indicates either a subacute stage of an infection, polyposis, or retention of secretions during an acute allergic exacerbation with marked obstruction. Lastly, Kully¹⁸⁹⁷ has recently shown that the

prolonged and excessive use of nasal vasoconstrictors may result in persistent changes in the mucous membrane accompanied by the presence of eosinophils in the secretions. The results of repeated cytologic studies are, therefore, to be interpreted only in correlation with the clinical symptoms, with the changes in the nasal mucosa, and with the bacteriology of the nasal membranes.

ETIOLOGIC DIAGNOSIS

The first and most important step in establishing the diagnosis is to take the case history painstakingly and patiently, for this purpose the physician may make use of the special questionnaire to be found in the Appendix. When there is reason to suspect an inhalant allergen, one may perform either a nasal or an environmental test—the latter consisting in exposing the patient to the suspected allergen (e.g., dust, flour) or pathergen (e.g., chemical, strong sunlight) at home or at his place of work. When the history does not incriminate any particular substance, skin tests with the scratch technic must be resorted to. If intracutaneous tests are preferred, they should be interpreted as specifically positive only if the skin reaction is followed by a focal (nasal) reaction. Moreover, Rudolph and Cohen,¹⁸⁹⁹ Dean et al.,¹⁸⁹⁹ and others have shown that skin tests are often negative, while direct nasal testing, either by insufflation or with the intramucous technic, evokes a positive reaction. When food allergy is suspected as the basis of the rhinopathy, elimination and trial diets are indicated.

Wherever there seems to be a possibility of a bacterial infection of the nose or of the paranasal sinuses, the physician should have a culture made of the secretions and perform skin tests with an autogenous vaccine. Furthermore, it is absolutely essential to have the patient examined by a competent rhinologist for any possible pathologic nasal condition that might otherwise be overlooked. At the same time, special attention should be given to the recognition of acute and chronic infections as possible complications of allergy.

¹⁸⁹⁷ KULLY, B. M.: *J. A. M. A.* 127: 307, 1945.

¹⁸⁹⁹ RUDOLPH, J. A., and COHEN, M. B.: *J. Allergy* 5: 475, 1934.
¹⁸⁹⁹ DEAN, L. W., LESTON, L. D., and LINTON, C. S.: *Ann. Otol., Rhin. & Laryng.* 48: 317, 1935.

Lastly, roentgenologic examination of the sinuses is desirable

Aside from these special allergic methods, every patient should be given a complete physical examination, including blood count and sedimentation rate. If indicated, endocrine studies are to be made and possibly also microscopic examination and culture of the stool.

As mentioned above, many cases of rhinopathy are not of the specific allergic but of the pathergic (nonspecific) type. That the differentiation between those two types is of decisive importance for the choice of therapy surely need not be stressed again.

6 THERAPY

Allergic and pathergic rhinopathy should be treated not only for themselves, but also as a prophylactic measure against asthma. Allergic coryza is frequently the forerunner of the latter, which means that the agent that causes the nasal allergy very commonly produces bronchial allergization sooner or later. Just as in the case of asthma, there is no standard treatment for rhinopathy. Whenever possible, each case is to be treated etiologically. Unfortunately, however, this approach is hardly possible in many cases.

In specific allergic rhinopathy, the measures to be considered depend upon the nature of the allergen. When the causal agent is an inhalant, hyposensitization is often successful. In this category, the best results are obtained in cases of dust allergy (for technic, see p. 238). Strangely enough, many patients with the clinical symptoms of house dust sensitivity who give negative reactions to both direct and indirect testing, benefit by the administration of autogenous house dust extract (Hansel¹⁹³⁹), success in treatment is dependent upon the determination of the optimum dose, which is often quite small. Shambaugh¹⁸⁷⁶ and others have also advocated low dosage therapy. Far less favorable are the results obtained in rhinopathy from flour, so commonly observed in bakers, millers, and cooks. In this condition, the senior author and Wiethe⁷⁹¹ achieved good results with intramucous injections into the nasal mucosa of the septum, producing a wheal similar to that obtained with the intracutane-

ous technic, weak concentrations and minute quantities (0.01 to 0.02 cc) are best used. To guard against the danger of a shock, small quantities of epinephrine (0.05 cc) may be added to the fluid to be injected. Hallermann⁷⁹⁵ likewise was able to achieve a complete cure with this method in a case of rhinopathy due to flour. In cases due to food allergy, elimination of the responsible food, oral deallergization, or the propeptan method will be of decided value.

In cases of bacterial allergy, subcutaneous desensitization with autogenous vaccine is often beneficial. There have been some attempts at local desensitization by means of an intranasal vaccine spray, based on the theory that tissue immunity depends on the local presence of specific antibodies and phagocytes called forth by the application of vaccine to the nasal mucosa. Walsh¹⁷⁰⁴ reported encouraging results with this technic.

Local or general chemotherapy constitutes another approach when infection is present. For the former, local instillation of a suspension of microcrystalline sulfathiazole (paredrine sulfathiazole suspension—Smith, Kline, and French) is of decided value in selected cases (Silcox and Schenck,¹⁹⁰¹ Fabricant¹⁹⁰²). Prothricin (Sharp and Dohme), containing 0.02 per cent of tyrothricin, is also useful. If local treatment is ineffectual, oral administration of sulfonamides (e.g., sulfathiazole, 1 Gm. every six hours for two days then 0.5 Gm. with the same time intervals for three more days) is advisable. Thereafter, treatment with vaccine should be instituted.

Rhinopathy based on endocrine disturbances may be managed by means of endocrine substitution therapy. Cases of hyperthyroidism or hypothyroidism are treated with measures appropriate to the condition.

In cases of rhinopathy due to intestinal dysfunction, the underlying constipation or enteritis must be corrected. If there is a faulty intestinal flora, a change by means of neocultol, resorcinol, or oral *Bacillus coli* preparations should be tried, as well as immunization with an autogenous stool vaccine. With the latter method the authors sometimes achieved striking

¹⁹⁰¹ SILCOX L. E., and SCHENCK H. P. Arch. Otolaryng. 36: 171, 1942.

¹⁹⁰² FABRICANT N. D. Am. J. 31: 56: 546: 1933.

ingly good results in appropriate cases. It should be particularly stressed that immunization procedures must be begun with small doses, in order not to induce severe focal or local reactions. In some instances observed by us, the patient was unable to tolerate doses of more than 1,000 organisms. Soricin may be of value.

Treatment is, of course, far more difficult when the cause of the rhinopathy cannot be discovered, or when the case is pathergic in character. In instances of this kind, local and general measures must be instituted. The former are intended to lower the usually non-specific hypersensitiveness of the nasal mucosa, and simultaneously to increase its resistance. In order to accustom the nasal mucosa to local irritation, the patient should be instructed to take appropriate breathing exercises three times daily (humming while standing, later while running, for three to ten minutes). Good results may occasionally be obtained by small doses of roentgen rays (150 r, filtered through 0.3 mm. of copper plus 1 mm. of aluminum, three times at intervals of one month). Jacquelin¹⁹⁰ recommends intramuscular injections of autogenous serum (see p. 209).

Of the general and systemic measures, old tuberculin has proved—in the writers' hands, at least—to be of definite value in cases in which there is a marked reaction to a small dose, such as 0.1 cc. of a 1:1,000,000 or 1:100,000 dilution. The technic of tuberculin therapy is given in detail in the section on asthma (p. 643). The results may perhaps be explained on the basis of a metallergic mechanism.

Another helpful method is treatment with histamine, as recommended by Farmer and Kaufman,¹⁹⁰³ and Williams,¹⁹⁰⁴ and confirmed by the present writers. The initial dose is 0.05 to 0.1 cc. of a 1:100,000 dilution (in terms of histamine base) or even of a 1:10,000 solution. The injections are doubled, if well tolerated, and given two or three times weekly in the beginning. Later they can be spread to approximately five-, seven-, ten-, fourteen-, and twenty-one-day intervals, attaining a maintenance dose which affords maximum

benefit, but not exceeding 0.1 to 0.3 cc. of a 1:1,000 dilution. However, it should be stressed that the dosage must be individualized.

According to Gant, Savignac, and Hochwald¹²⁷ oral administration of histamine produces immediate symptomatic relief. Contrary to general belief, they contend that the drug given by mouth is promptly absorbed and produces the same physiologic effect as when given parenterally. The method is not one of "desensitization," but of symptomatic control.

TECHNIC The initial dose is 1 drop of a 1:1,000 dilution in a glass of water on an empty stomach (before meals). If the dose is too large in a given case, it will aggravate the symptoms and if too small, will have no effect. The correct dose relieves the patient within fifteen to twenty minutes. If no untoward effects are noted, the patient is advised to increase the dosage 1 drop each day until toxic reactions appear. Thereafter, he is given a maintenance dose just below the toxic level. This may vary from 1 drop of the 1:1,000 dilution to 25 drops of a 1:100 dilution, the average being 5 to 7 drops of 1:1,000. It is important to find the proper dose for each individual since there is a wide variation in patients' susceptibility to histamine. When symptoms recur after any dose, another is taken, with the same effects. Patients usually require six to eight doses daily at first, but after a few weeks of treatment only two or three doses daily, and later only an occasional dose every few days.

We have extensively used histamine hydrochloride 1:1,000 dissolved in 20 per cent alcohol, and had satisfactory results in a goodly percentage of cases of the pathergic type of rhinopathy.

Histamine-azoprotein (hapamine) injections may be tried in selected cases, but with great care.

Favorable effects are occasionally obtained with dietetic measures. The diet should be poor in salt and liquids, and should be maintained for many weeks. It is advisable to begin with two or three days of a diet consisting only of a little fresh fruit and water. Furthermore, general strengthening and tonic measures should be instituted. Attention to adequate rest and elimination, and relief of pain and apprehension by analgesics and sedatives should not be neglected in view of the alleviation they afford. Physiotherapeutic measures, including application of heat or infra-red rays, and occasionally of cold, often give prompt relief. Psychotherapy, in re-

¹⁹⁰³ FARMER, L. and KAUFMAN, R. E. *Laryngoscope* 52: 255, 1942

¹⁹⁰⁴ WILLIAMS, H. L. *Ann. Otol., Rhin. & Laryng.* 53: 397, 1944

moving emotional tension and strain, has a definite place in resistant cases

The symptomatic treatment employs the following drugs ephedrine (0.025 to 0.045 Gm, or $\frac{1}{4}$ to $\frac{3}{4}$ grain) may be given three or four times daily. In order to obviate its exciting effect, it is often combined with phenobarbital (0.008 to 0.015 Gm, or $\frac{1}{8}$ to $\frac{1}{4}$ grain). Other sympathomimetic drugs may be used. Nethamine was successfully employed by Friedman and Cohen,⁸³¹ and in combination with acetophenetidine by Craddock.^{190a} In cases of severe rhinorrhea, repeated doses of atropine (0.12 to 0.2 mg, or $\frac{1}{80}$ to $\frac{1}{40}$ grain) or belladonna (0.005 to 0.01 Gm, or $\frac{1}{40}$ to $\frac{1}{20}$ grain of the extract) may be beneficial. Bellergal (1 tablet two or three times a day) helps to overcome emotional or autonomic instability and promotes mental rest. Calcibronat (10 cc intravenously or 1 tablespoonful of the granules, three times a day) lessens the irritability of the neurovegetative system. Niacin (nicotinic acid) by subcutaneous injection for a few days in doses of 25 to 100 mg, followed by daily oral administration, is recommended by Williams.¹⁹⁰ⁱ Nicotinamide is ineffective.

For local symptomatic therapy, vasoconstrictors are of distinct value. This group includes ephedrine sulfate (2 per cent), neo-synephrin hydrochloride (1 per cent), propadrine hydrochloride (1 to 3 per cent), and privityne hydrochloride (0.1 per cent). A benzedrine (amphetamine) inhaler may also be used. Patients differ in their subjective responses to various preparations and often express pronounced preferences.

Fabricant^{190e} pointed out that a valuable function is performed by nasal decongestants that lower the nasal pH from the abnormal alkaline state obtaining during the more active phases of an allergic rhinitis, toward a desirably normal acid state (pH approximately 5.5 to 6.5). For this purpose he advocates ephedrine sulfate in an isotonic solution of dextrose such as glucofedrin, or a buffered solution such as privityne.

The solutions above instanced may be sprayed into the nares by means of an atomizer

or instilled by means of a dropper. For particularly effective and widespread contact with the nasal mucosa, the Parkinson¹⁹ method is recommended both for office treatment and for administration at home.

TECHNIC. The patient assumes the lateral head low posture shown in FIGURE 241 by lying placed side wise on a table or bed with the lower shoulder supported by a few pillows. Then one or two droppersful are instilled into the lower nostril. With the head in this position below the shoulder and slightly forward the solution will neither flow out of the nares nor enter the pharynx. After three or four minutes the head is rotated anteriorly the solution is permitted to flow into a towel and the remainder is gently blown out.



FIG 241 LATERAL HEAD LOW POSITION FOR INSTILLATION OF NOSE DROPS (PARKINSON METHOD)

Then the patient is placed on his other side and the opposite passage is treated. The solution flowing into the upper straits of the nose and shrinking the middle turbinates enters the middle meatus and reaches the ostia of the maxillary frontal and anterior ethmoid sinuses. This procedure may be repeated every few hours and promotes prolonged nasal ventilation.

The Proetz position may also be used.

TECHNIC. The patient lies on his back with his head hanging far down over the side of a bed, the chin and the external auditory meatus being in the same vertical plane. The drops are inserted in both nostrils and the position maintained for a few minutes the head being turned slowly from side to side as far as possible. The patient then sits up and lowers the head forward holding this position for one half minute.

In order to prevent contamination of the contents of the bottle containing the nose drops (Gompertz and Michael^{190b}), the following precautions should be carried out

^{190a} CRADDOCK W. H. J. Med. (Cincinnati) 22: 456 1941.

^{190e} FABRICANT N. D. Eye Ear Nose & Throat Monthly 25: 219, 1944.

^{190b} PARKINSON S. N. Arch. Otolaryng. 17: 787 1933.

^{190c} GOMPERTZ J. L. and MICHAEL P. J. A. M. A. 119: 1287 1942.

The dropper should be filled from a teaspoon or other container into which the quantity of fluid needed for one treatment has been poured. The screw cap should be replaced immediately. The dropper is not to be inserted in the bottle, any unused solution is not to be returned to the bottle. After use the dropper should be thoroughly washed in hot water or sterilized. A separate dropper should be provided for each patient.

The limitations and disadvantages of nasal vasoconstrictive medications* have been the subject of increasing attention, most recently by Sternberg,¹⁹⁰⁹ Gollom,¹⁹¹⁰ Kully,¹⁹⁰⁷ and Feinberg and Friedlaender.¹⁹¹¹ Most emphasis has been the secondary vasodilation or "reflex rebound" noted to follow the subsidence of the initial vasoconstriction, and often to exceed it in degree and duration. This is said to occur with any of the sympathomimetic drugs, but more frequently with some than with others. As a result of this compensatory swelling of the mucosa, involving especially the deeper venous sinuses, the patient's discomfort may be increased and drainage further impeded. Injudicious use of nose drops may produce a type of rhinopathy which is indistinguishable, even cytologically, from that due to allergy. Moreover, allergic rhinopathy may be made more severe, and the membranes may become refractory to further therapy. There is a distinct tendency on the part of some patients to abuse these drugs and to employ them excessively—a sort of addiction—with a resulting vicious cycle. Used in these quantities they may also elicit the same central nervous system effects as when the drugs are administered internally. The inclusion of antiseptics and sulfonamides is said to increase their irritant properties without compensatory therapeutic benefits. Regardless of the cause, the management consists, of course, in the complete discontinuance of all intranasal therapy, following which the nasal congestion disappears usually within a week. Lastly, Waring¹⁹¹² has described three cases of marked sedation produced by the intranasal instillation of praline in children.

* It should be made clear that we are not here referring to those nose drops which owe their deleterious effects to alkalinity, lack of isotonicity, or undesirable influence on ciliary action, but to those commonly considered acceptable.

¹⁹⁰⁹ STERNBERG, L. New York State J. Med. 44: 1573, 1944.

¹⁹¹⁰ GOLLOM, J. Canad. M. A. J. 51: 123, 1944.

¹⁹¹¹ FEINBERG, S. M., and FRIEDLAENDER, S. J. A. M. A. 128: 1095, 1945.

¹⁹¹² WARING, J. I. ibid. 129: 129, 1945.

Another symptomatic local approach consists of intranasal ionization with zinc sulfate. In contrast to the situation in hay fever, in which this method is definitely inferior to specific treatment, ionization may under certain conditions be employed in the treatment of pathergic rhinopathy (Dean¹⁹¹³). According to Alden¹⁹¹⁴ and Hansel,¹⁹¹⁵ ionization should be instituted only in cases in which other methods of treatment have failed to produce satisfactory results, in which obstruction is predominant, and where the mechanical relief to be expected is commensurate with the tissue damage incident to ionization. The value of ionization consists in reducing excessive nasal intumescence and hypersecretion. Lastly, it should be added that this method is to be undertaken only in expert hands. (Concerning the hazards and unpleasantness connected with this therapy, see p. 560.) Chemical cauterization with phenol, trichloroacetic acid, and silver nitrate, and submucous diathermic coagulation belong to this same group of therapeutic measures.

The question of *nasal surgery* still remains to be discussed. The fact that very many of the patients who consult the allergist for treatment of rhinopathy have previously been subjected to one or more operations, such as removal of nasal polyps, submucous resections, turbinectomies, sphenoethmoid exenteration, intranasal antral window and radical sinus operations—for instance that of Caldwell-Luc—shows in itself that nasal surgery is frequently of no value. Thus, Piness and Miller¹⁹¹⁶ report that among 843 patients suffering from hay fever, vasomotor rhinitis, or asthma, nasal operations proved to be completely futile in 413 instances. Of 500 cases with sinusitis, chronic tonsillitis, or abscessed teeth, studied by Weille,¹⁹¹⁵ 210 were operated on and the remainder treated conservatively. The results were about the same in both groups. According to Clarke and Rogers,¹⁹¹⁴ 73 per cent of their patients with rhinopathy had had one, and 20 per cent had had two or more operations without any lasting effect. In the senior author's series¹⁹¹³ of 73 patients, 21 had undergone a variety of nasal operations, practically

¹⁹¹³ DEAN, L. W. Ann. Otol., Rhin. & Laryng. 45: 326, 1936.

¹⁹¹⁴ ALDEN, A. M. Laryngoscope 47: 17, 1937.

¹⁹¹⁵ HANSEL, F. K. Arch. Phys. Therapy 19: 489, 1938.

¹⁹¹⁶ WEILLE, F. New England J. Med. 215: 250, 1936.

without any benefit, in some instances, the operations had even proved to be harmful.

In an excellent presentation of the problem of surgical treatment of the nose in allergy from the standpoint of a rhinologist, Hansel¹⁹¹⁷ makes the following statement: "All operative procedures on the nose and paranasal sinuses should be performed with the idea of restoring function and eliminating infection, basing the indications upon existing symptoms and pathologic changes, just as if an allergic condition did not exist. Although rather marked pathologic changes may exist in the nose and paranasal sinuses in allergy, they may subside under allergic management and may not require operative procedures." An operation should not be performed during an acute attack, since the condition is always exaggerated at this time and is therefore likely to be overestimated.

Each case is an individual problem, consequently, no specific rules can be formulated as to the indications for conservative or radical surgery on the nose or paranasal sinuses. Operative procedures are justified if the pathologic condition persists after appropriate anti-allergic therapy. The indications for the removal of nasal polyps are based upon their degree, size, and chronicity. Under allergic management, nasal polyps may show a marked decrease in size or even disappear completely. But if, on the other hand, the polypoid formations are of the permanent type, producing obstruction and retention of secretion, and thus promoting secondary infection, they should be removed. Since nasal polyps and polypoid tissue very often represent an allergic condition of the mucous membranes—i.e., a result and not a cause of rhinopathy (Hastings,¹⁹¹⁸ Trasoff,¹⁹¹⁹ Kern and Schenck,¹⁹²⁰ Hansel¹⁹¹⁷)—one must not be surprised to see that the polyps, once removed, very frequently reappear. When the cause of an allergy is known (e.g., hypersensitivity to flour), cautious direct injections of the allergen into the polyps can, as Urbach and Wiethe¹⁹³¹ have shown, cause them to disappear.

A submucous resection of the nasal septum is indicated in those cases in which there is a very pronounced deviation, producing serious obstruction and predisposing to sinus infection. A resection is not necessary, however, if the obstruction is relieved by control of the allergic symptoms.

In summary, it may be reiterated that the indications for operations upon the nose in allergic patients should be based on the same principles as in the case of nonallergic individuals.

The writers are of the opinion that the methods outlined in this section will benefit and even cure a great percentage of rhinopathy cases. It is always decidedly helpful if more severe cases can be hospitalized, in order that all the necessary examinations and tests may be performed as efficiently and promptly as possible.

B ALLERGIC SINUSITIS (ALLERGIC SINUSOPATHY)

The term sinusitis designates any inflammation of the mucosa of the nasal accessory sinuses. The acute fulminating type cannot be confused with an allergic condition, and therefore need not be discussed here. The pathogenesis of the subacute and chronic forms, on the other hand, is quite frequently rather difficult to differentiate. The following possibilities are to be considered: (1) infectious (primary suppurative) sinusitis, (2) allergic sinusitis, (3) allergic sinusitis complicated by secondary infection, (4) pathergic sinusitis, (5) pathergic sinusitis complicated by secondary infection.

1 PATHOGENESIS

INFECTIOUS SINUSITIS

The infectious form of sinusitis is caused by bacterial invasion of the mucous linings of the paranasal sinuses, either by contiguity from the nasal membranes or hematogenously. This often follows a common cold, which, while due to a virus, may pave the way for invasion by micro organisms or for an increase in virulence of the saprophytes already present. Sinusitis so caused frequently persists long after the acute rhinitis subsides, and in many cases becomes subacute or chronic. According to

¹⁹¹⁷ HANSEL F K. Ann Otol Rhin & Laryng 45: 111 1936

¹⁹¹⁸ HASTINGS H. Arch Otolaryng 12: 499 1930

¹⁹¹⁹ TRASOFF A. Laryngoscope 43: 531 1933

¹⁹²⁰ KERN R A and SCHENCK H P. J A M A 103: 1293 1934

M. Clin North America 22: 1633 1938

Turnbull,¹⁹²¹ cultures reveal that the predominating bacteria are *Staphylococcus aureus* or *Staph. albus*, hemolytic or nonhemolytic, and sometimes *Streptococcus hemolyticus* alpha or, rarely, beta. Semenov¹⁹²² found that cultures from the tissues of chronic sinusitis gave evidence of mixed infections in the large majority of instances, and that streptococci, particularly the hemolytic types, predominated, frequently in combination with staphylococci, *Micrococcus catarrhalis*, pneumococci, Friedlaender's bacilli, influenza bacilli, colon bacilli, diphtheroids, and Streptothrix.

ALLERGIC SINUSITIS

This is nearly always found in association with allergic rhinopathy and will be found to share the same etiologic agents in a given case. Furthermore, it will often be present in cases of asthma. It is now generally agreed that both the sinus and bronchial involvements are parts of a syndrome that depends fundamentally on the same mechanism, and that sinusitis is only occasionally the cause of an asthmatic condition (Rackemann and Weille¹⁹²³). This explains why operations for sinus conditions scarcely ever alleviate the asthma in such cases. Allergic sinusopathy and bronchial asthma may occur simultaneously, or may alternate with each other, or may replace each other. They differ only in that the allergen acts on different shock structures. Rackemann and Tobey¹⁹³⁰ found sinusitis in 25 per cent of a large series of asthma cases, other authors, including Cooke, Vaughan, and Kelly, reported a much higher incidence (between 65 and 89 per cent), their figures being based, however, on the results of X-ray examinations. A somewhat different figure is arrived at when one determines the frequency of asthma in a series of rhinopathy cases (Rackemann,²⁹ 16 per cent, Bullen,¹⁹²⁴ 12.5 per cent).

In addition, it may be mentioned that the average incidence of polyposis in sinusopathy, and including other types of nasal allergy, is about 25 per cent (Hansel).

As might be expected, allergic sinusitis is often complicated by secondary infection due

to the saprophytic bacteria constantly present in the nasal passages. This is a particularly common occurrence after acute coryza. If the immunity mechanisms are adequate, the infection will regress, leaving the previous picture of an allergic sinusopathy. In many cases, however, the micro-organisms will gain the upper hand and bacterial hypersensitiveness will be more or less permanently established. The significance of this complication lies in the fact that infectious processes of this kind cannot be cured until the underlying allergic condition is identified and corrected (Cooke¹⁹²⁵).

PATHERGIC SINUSITIS

This condition represents a nonspecific hypersensitiveness of the mucous membranes of the paranasal sinuses and is often associated with pathergic rhinopathy. It is caused by the same multiple factors as the latter condition, including sudden changes in temperature, exposure to cold wind, strong vapors, smoke, and mechanical irritants. A very important factor is secondary invasion by bacteria that find conditions in the already inflamed mucosa favorable to their propagation, particularly if aeration and drainage are impeded by closure of the ostia owing to swelling of the membranes.

The incidence of the various types depends largely on the investigator's material. Allergists will see the allergic and pathergic forms more frequently, while rhinologists will encounter more of the infectious cases. In a study based on examination of 150 specimens from operated cases of sinusitis, Ash¹⁹²⁶ was able to classify them as 75 infectious, 28 allergic, and 47 mixed. In this series, hyperplastic changes were observed more frequently than any other pathologic feature in cases of sinusitis of the infectious type, and polyps most frequently in cases of allergic origin. On the other hand, polyps may develop secondarily in a primarily suppurative sinusitis. Polyps due to infection are firmer than those caused by allergy. In a similar study of the microscopic pathology of the surgical specimens from 500 cases of chronic sinus disease of sufficient severity to require operation, Semenov¹⁹²²

¹⁹²¹ TURNBULL, F. M. J. A. M. A. 116: 1929, 1941.

¹⁹²² SEMENOV, H. *Ibid.* 114: 2159, 1938.

¹⁹²³ RACKEMANN, F. M., and WELLS, F. L. *Arch. Otolaryng.* 30: 104, 1939.

¹⁹²⁴ BULLEN, S. S. J. Allergy 4: 402, 1933.

¹⁹²⁵ COOKE, R. A.: *Laryngoscope* 40: 210, 1930.

¹⁹²⁶ ASH, J. E. *Tr. Am. Acad. Ophth.* 44: 304, 1939.

found manifest evidence of allergy in 17 per cent, and tissue eosinophilia along with other histopathologic signs sufficient to warrant a presumptive diagnosis of latent allergy in another 35.4 per cent. Allergic sinusopathy is characterized by mucoid degeneration of the epithelium, hyalinization of the basement membrane, pronounced polypoid edema of the submucosa, and eosinophilia of the tissues. Degenerative changes (retention cysts, mesothelial cysts, polyps) are most marked in allergic persons.

There is no general agreement as to the etiology of chronic hyperplastic sinusitis. While Pinness and Miller, Hansel, Dean, Semenov, and others are of the opinion that allergens are the primary causal factors and that the infection is to be regarded as secondary, another group of authors, including particularly Grove and Cooke,¹⁹⁰⁷ hold that the bacterial infection is primary and in itself brings on a bacterial hypersensitiveness that is expressed by these hyperplastic changes. These authors base their opinion on (1) the frequency of recovery of organisms from the membranes, (2) the fact that strictly allergic cases without infection rarely show hyperplastic changes, and (3) the fact that autogenous vaccines evoke local exacerbations in the sinuses, with marked edematous swelling, accompanied by an outpouring of mucopurulent secretions containing numerous eosinophils. Mullin¹⁹²⁸ found allergy present in 30 to 35 per cent of all cases of chronic infection of the sinuses, and McHenry¹⁹²⁹ in 23 of 80 cases of chronic maxillary sinusitis requiring an antral window operation.

2 SYMPTOMATOLOGY

It need only be mentioned here that the changes found in the paranasal sinuses are inflammatory in character, and can be divided into the hyperplastic and the suppurative types. The former is far more commonly encountered, and is characterized by an inflammatory thickening of the mucous membrane, usually associated with polyp formation. The suppurative type may be either acute or chronic. The acute forms are accompanied by

high fever and severe systemic symptoms. The chronic cases are characterized by dull headaches and occasionally mild systemic manifestations, such as malaise and low grade fever. However, both Thornell¹⁹³⁰ and Shafran¹⁹³¹ warn that a clinical diagnosis of 'sinus headache' can only rarely be supported by objective evidence of chronic purulent sinusitis, and that postnasal drip and headache are prominent symptoms of allergic rhino sinusitis and nasal psychoneurosis. For details concerning the symptoms—which depend on whether the frontals, antra, sphenoids or ethmoids are involved separately, or whether several or all of them are affected together (pansinusitis)—the reader is referred to text books on rhinology.

3 DIAGNOSIS

Since some systemic disorders and certain local conditions entirely unrelated to the paranasal sinuses may present similar symptoms, it is absolutely essential that the patient be given a thorough medical examination and a diagnostic study. Among various conditions that sometimes simulate sinus disease are psychoneurosis, endocrine disturbances, dental infections, malocclusions, refractive errors, and eyestrain. The diagnosis of nasal psychoneurosis is in need of more widespread recognition and application, and frequently presents diagnostic difficulties. Sometimes objective nasal pathology is present but the subjective complaints are usually entirely disproportionate to the objective changes found.

A useful method for differentiating between infectious and allergic sinusitis consists of cytologic studies of the nasal secretions (see p. 494); these, however, must be performed repeatedly. While pus cells and bacteria are found in abundance in the infectious types, a smear made from the nasal discharge or from sinus washings in the allergic forms often shows a predominance of eosinophils. However, the situation becomes more complicated in the mixed types.

Röntgenologic examinations of the sinuses should be carried out in every case. The advantages of this are that the clinical diagnosis can be confirmed, and that sometimes it is

¹⁹⁰⁷ GROVE C. R. and COOKE R. A. *Arch. Otolaryng.* 18: 622, 1933.

¹⁹²⁸ MULLIN W. V. *S. Clin. North America* 15: 839, 1935.

¹⁹²⁹ MCHENRY L. C. *Southern M. J.* 36: 18, 1933.

¹⁹³⁰ THORNELL W. C. *Proc. Staff Meet. Mayo Clin.* 19: 470, 1934.

¹⁹³¹ SHAFRAN L. *Stanford M. Bull.* 2: 123, 1934.

able to disclose pathologic changes not revealed on direct inspection and transillumination. However, "most radiologists will readily admit that in the entire field of roentgenology nothing affords them greater difficulty than examination of the paranasal sinuses" (Kornblum¹⁹³²). Kornblum, one of the leading students of sinus radiology, amplified this statement by the admirably frank confession that

the same radiologist a few weeks later will frequently result in a different interpretation. In addition to these difficulties of interpretation, X-ray conclusions are often unreliable because of the high incidence of positive findings in apparently normal individuals, particularly on the eastern seaboard. It should be borne in mind that quite often roentgenologic changes are merely evidence of past disease rather than



FIG. 242 ACUTE SUPPURATIVE SINUSITIS OF RIGHT ANTRUM, WITH THICKENING OF MUCOUS MEMBRANE OF LEFT (Courtesy Dr. K. Kornblum)

independent readings of the same sinus film by three highly skilled men at the University of Pennsylvania (Dr. H. K. Paucoast, Dr. E. P. Pendergrass, and himself) were seldom in complete agreement. If this is so, how much greater must be the variation in interpretation among roentgenologists and allergists of unlike training, working under different conditions and using different technics. Moreover, Kornblum pointed out that a rereading of a film by

of present pathology. Moreover, there are many instances in which X-ray involvement of the sinuses is not accompanied by symptoms and is therefore of no clinical importance. Despite all these drawbacks, roentgenologic investigation is nevertheless of distinct value if correlated with history, physical examination, and allergic and laboratory studies.

The chief value of X-ray examination in sinusitis is that it helps to differentiate between the chronic infectious and the allergic

¹⁹³² KORNBLUM, K.: *Am. J. Roentgenol.* 38: 43, 1937

types although this is by no means always possible. A slight general haziness usually indicates thickening of the lining membrane suggesting either allergic edema or a low grade infection while a dense shadow that completely obliterates the area generally denotes suppuration (empyema) granulation or tumor. The last three are as a rule roentgenologically

the Mayo Clinic H. P. Johnson observed that 35.9 per cent of the maxillary sinuses that showed shadows in the roentgenograms did not contain pus when irrigated whereas in 25.3 per cent of those without shadows pus was obtained on puncture. This may be explained in part on the basis of the fact that positive findings may represent evidence of a past rather



FIG. 243. POLYP IN RIGHT ANTRUM WITH SLIGHT HAZINESS IN LEFT

(Courtesy Dr. K. Kornblum)

indistinguishable. Occasionally when the film is taken with the patient in the upright position a fluid level may be visualized indicating the presence of pus (Fig. 242). Polyps in the antra and frontal sinuses are sometimes recognizable on the pictures as rounded areas of slightly increased density (Fig. 243). Furthermore the swollen and congested mucous linings in a case with acute or subacute allergic changes (Fig. 244) may give shadows simulating those seen in chronic sinus infections (Fig. 245). Thus in 300 consecutive cases at

than of an existing pathologic condition while negative findings suggest that soft tissue involvement of the paranasal sinuses often can not be demonstrated without the instillation of some radiopaque substance.

There are however two ways of increasing the usefulness of the X-ray method: (1) repeating the examination after a few days—thus if the first picture shows a sinus cloudy to the point of simulating polyp formation while in the second picture taken one week later it appears normal an allergic disorder (transi-

tory edema) may be strongly suspected, and presence of an infection ruled out, (2) filling the sinuses with a radiopaque substance by the displacement method of Proetz¹⁹³³—in allergic conditions the shadow is not so dense, but ballooned rather than pebbled, and usually does not follow the bone outline as it does in infections of the lining membranes.

Finally, it must be reiterated that X-ray

metry of the two sinuses or other anatomic variations, by a difference in the thickness of the bones, and even by a slight infiltration of the soft parts. Transillumination often fails to show evidence of polyps or mucus, since light may be transmitted through them; but it will reveal an accumulation of pus. In conclusion, transillumination may give a rough idea of the more marked changes present.



FIG 244 CLOUDINESS OF RIGHT FRONTAL AND LEFT ETHMOID SINUSES DUE TO ACUTE ALLERGIC PROCESS (Courtesy, Dr K Kornblum)

findings may be relied upon only when carefully correlated with those of the clinical examination, the history, and cytologic investigation and bacteriologic study of the secretions from the nose and the paranasal sinuses.

Transillumination of the sinuses is less dependable, since a difference in the opacity of the maxillary sinuses, for example, can be caused not only by disease, but also by asym-

4 THERAPY

Methods of treatment of sinusitis have undergone some important changes in the past few years. It is now generally recognized that allergic management must be given a fair and thorough trial before any surgical approach is justified, provided, of course, that there is no acute need for intervention. Cooperation between rhinologists and allergists will, as shown by Woodward and Swineford,¹⁹³⁴ achieve very

¹⁹³³ PROETZ, A. W. The Displacement Method of Sinus Diagnosis and Treatment. St. Louis: Annals Pub. Co., 1931.

¹⁹³⁴ WOODWARD, F. D., and SWINEFORD, O. Arch. Otolaryng. 34: 1123, 1941.

satisfactory results. Allergic treatment both specific and nonspecific along the lines discussed in the preceding section on rhinopathy joined with conservative rhinologic measures has to a very large extent replaced the various operative procedures of a radical and semi-radical nature. But if an operation is necessary the modern concept demands establishment of ventilation and drainage of the

constrictors into the nose in the lateral head low position (p. 498) or by the displacement method (Proetz¹⁹³³ Gundrum¹⁹³⁵ Gewanter¹⁹³⁷).

TECHNIC OF THE DISPLACEMENT METHOD. After the nasal mucosa has been shrunk by the application of a vasoconstrictor solution and the patient has cleared his nose by gentle blowing he is placed on his back with the head hyperextended over the end of an examining table or cot so that the chin and the external auditory



FIG. 245. CLOUDINESS OF RIGHT ANTRUM PROBABLY DUE TO HYPERPLASTIC CHANGES IN MUCOUS MEMBRANE. LEFT ANTRUM NORMAL.

(Courtesy Dr. K. Kornblum)

sinuses. However, due care should be exercised to interfere as little as possible with the physiologic functions of the nose and sinuses. A short discussion of the surgical approach will be found on page 499.

The conservative measures comprise local as well as general procedures. A useful guide to the former is Fabricant's monograph.¹⁹³⁵ Local therapy includes instillation of vaso-

meatuses are in the same vertical plane. With the patient breathing quietly through the open mouth 2 or 3 cc. of a weak vasoconstrictor (0.25 or 0.5 per cent ephedrine sulfate in isotonic sodium chloride solution) are then instilled into each nostril. In some cases larger quantities are necessary. Intermittent negative pressure (approximately 180 mm. of mercury) is applied to one nostril by means of a bulb syringe or one of its modifications while the operator's finger closes the other and the patient closes the pharynx by saying "kay" or "cake" a number of times. Followings x to

¹⁹³⁵ FABRICANT, N. D. *Nasal Medication*. Baltimore: Williams & Wilkins, 1942.

¹⁹³³ GUNDRUM, L. K. *Laryngoscope* 58: 949, 1940.

¹⁹³⁷ GEWANTER, R. *Arch. Otolaryng.* 32: 728, 1943.

ten alternating suction applications, the patient is allowed to sit erect for ten minutes, and the same instillation-suction procedure repeated. While a weak, dilute, isotonic, slightly acid nasal vasoconstrictor is the most satisfactory, there are advocates of other preparations, such as penicillin, bacterial antigens, lysates, polyvalent antiviral, and bacteriophage.

Others recommend nasal spray twice daily with paredrine-sulfathiazole suspension (Silcox and Schenck,¹⁹⁰¹ Sulman¹⁹³⁹) and similar sulfonamide preparations, careful nasal suction, and irrigation of the sinuses. The untoward effects following abuse of vasoconstrictive medications have been mentioned in the previous section.

Recently, intranasal instillation of penicillin solutions (250 to 500 Oxford units per cc.) has gained an increasing number of adherents for cases with evidence of infection. Tyrothricin (prothricin—Sharp and Dohme) is also effective.

Infra-red irradiation and short wave diathermy are useful adjuncts to other treatment after adequate drainage has been established. The latter is of value in the prompt relief of pain. The frontal and maxillary sinuses are the ones most suitable for treatment.

Butler, Greenwood, and Ivy¹⁹¹⁹ reported successful therapy of subacute and chronic sinusitis by repeated exposure to reduced atmospheric pressure in a decompression chamber of the type used in studies of aviation medicine. The pressure was rapidly reduced to 522.6 mm. of mercury, equivalent to ascent to an altitude of 10,000 feet. Rapid "ascent" was alternated with slow "descent" to 5,000 to 6,000 feet for a period of forty minutes, and the treatment terminated with slow recompression. Patients were treated twice a week, receiving an average of 18.1 treatments each. In addition to symptomatic benefit, there was rhinologic and roentgenologic evidence of improvement.

Another local method is X-ray therapy, the value of which is, however, the subject of some controversy. To mention only the most recent literature, Dysart¹⁹¹⁰ and Williams and Popp¹⁹¹¹ reported favorable responses in acute

types, and Christensen¹⁹¹² excellent results in subacute and chronic hyperplastic varieties, employing a specially designed cone and filter. In the treatment of chronic cases, according to Gatewood,¹⁹¹³ roentgenologic treatment is still in the experimental stage. Kornblum¹⁹⁴⁴ points out that the results achieved depend on the pathologic type of the sinusitis treated, as well as on the dosage employed. X-ray therapy in small doses (not exceeding 50 r) is frequently helpful in treatment of acute forms, since pain and headache are often relieved. Inasmuch as this is accompanied by an appreciable increase in the nasal discharge, the effect of roentgen therapy on the sinuses may be due to a decrease in the engorgement of the nasal mucosa. In the subacute types with nasal obstruction, persistent nasal discharge, and occasional headache, similar favorable results may be obtained. In chronic hyperplastic forms with exacerbations, the response is only fairly satisfactory, while in chronic types with extensive fibrosis as well as with polyps and cysts, nothing can be achieved.

While no uniform technic exists, the following method may be employed: 130 kilovolt peak, 5 milliamperes, 0.5 mm. copper and 1 mm. aluminum filtration, and 30 cm. skin target distance. One large anterior portal is used. A dose of 100 r is given once a week for four weeks and then every two weeks for a total of eight treatments, except in acute sinusitis, in which 50 r is given only once or twice. For children the filtration is 4 mm. aluminum and the dosage is 75 to 100 r once a week for four to six treatments. Eyebrows, eyelashes, and hair must be adequately protected.

General treatment can be carried out in different ways. Symptomatic treatment includes chiefly the administration of ephedrine-phenobarbital compounds (see p. 226). Systemic administration of penicillin or sulfonamide compounds in the initial stages of acute suppurative sinusitis or in the control of secondary infection of other types is often followed by marked relief. They are likely to be disappointing in the chronic varieties. Since patients with rhinopathy and sinusitis lose considerable amounts of nucleoproteins in their

¹⁹⁰¹ SULMAN, L. D. *Ibid.* 37, 713, 1943.

¹⁹¹⁰ BUTLER, D. B., GREENWOOD, G. J., and IVY, A. C. *Ibid.* 40: 266, 1944.

¹⁹¹¹ DYSART, B. R. *Ann. Otol., Rhin. & Laryng.* 43: 433, 1939.

¹⁹¹² WILLIAMS, H. L., and POPP, W. C. *Ibid.* 49: 719, 1940.

¹⁹¹³ CHRISTENSEN, F. C. *Radiology* 43: 21, 1944.

¹⁹⁴⁴ GATEWOOD, E. T. *Arch. Otolaryng.* 31: 275, 1940.

¹⁹⁴⁴ KORNBLUM, K. *Ann. Otol., Rhin. & Laryng.* 50: 533, 1941.

discharges, Howe¹⁹⁴⁵ recommended a diet rich in nucleoproteins, such as lean meat and all glandular tissues, and 0.65 to 1.0 Gm of nucleic acid in water, milk, or orange juice twice a day before meals.

In cases with a preponderantly staphylococcal infection, a course of staphylococcus toxoid injections is often of definite value (Woodward¹⁹⁴⁶). The efficacy of vaccines (both autogenous and stock) is still uncertain. Personally the writers are inclined to use autogenous vaccines in small dosage, provided there is a definite focal or general response to intracutaneous injection of 1,000,000 to 5,000,000 organisms. Walsh's intranasal vaccine spray method¹⁹⁰⁴ was discussed on page 496. Mention should also be made of the use of a stool vaccine in cases with a faulty intestinal flora, if its specificity is confirmed by focal or general reactions to small doses. Vaccine therapy is, of course, of no benefit to patients suffering from chronic sinusitis with poor drainage or none at all, or when the sinusitis is secondary to an untreated primary focus of infection, such as diseased tonsils (Solis-Cohen¹⁹⁴⁷).

C HAY FEVER (POLLINOSIS)

1 HISTORICAL INTRODUCTION

The physicians of antiquity and of the Middle Ages were well aware of the fact that many persons are seized by attacks of uncontrollable sneezing in the presence of certain plants (Galen, A.D. 200, Botallus, 1565, Benningerus, 1673, and others). Roses, lilacs, lilies, and linden and many other kinds of trees, as well as bushes and flowers—all have been mentioned, time and again, as being directly responsible for headaches, nasal itching, sneezing attacks, and distressing "dryness" of the respiratory passages, as well as asthma. It is very doubtful, however, whether all the manifestations described were identical with the condition under consideration here.

It was not, however, until early in the last century (1819), that the English homeopath John Bostock reported his own symptoms, at a meeting of the London Medical Society, in a paper entitled "Case of a Periodical Affection

of the Eyes and Chest." He thus became the first to publish a description—and, indeed, the classic description—of this disease. In 1828 he published another communication "Catarrhus Aestivus or Summer Catarrh" in which he first employed the term 'hay fever,' then in common use in southern England, he definitely rejected however, the idea of any relationship between the condition and hay itself or any other plant. On the other hand, Gordon first mentioned "hay asthma" in 1829, and attributed the difficulty in breathing to the aroma of blooming grasses, notably of sweet vernal grass. Elliotson, in 1831, pointed out that the clinical symptoms, including dermatitis, that follow contact of the hands with flowering grasses, were attributable not to hay but in all probability to the pollens of these grasses.

During the succeeding four decades, a number of authors devoted themselves to the task of confusing Bostock's "summer catarrh" with other forms of catarrh and asthma, completely ignoring its outstanding characteristic—the annual recurrence of the symptoms at a certain time of the year. Bostock's views did find some support, particularly from that forthright and enthusiastic investigator, Phoebus (1862), the great majority of physicians, however, denied that there was any justification for considering so called Bostock's catarrh as an independent entity, with the result that all of Bostock's work seemed to have been done in vain. However, it was another English homeopath, Blackley of Manchester, who on the basis of fundamental and truly inspired investigations on himself (1875) advanced proof of the fact that hay fever is due to pollen. Blackley was the first to evoke hay fever manifestations in himself and in other predisposed individuals by sniffing the "dust" of blossoms; he was also the very first to perform allergic skin tests (thirty years before von Pirquet), for he succeeded in showing that application of pollen to a scarified skin site resulted within a few minutes in severe itching, edematous swelling, and sometimes even in nasal manifestations as well.

Although these observations were absolutely sound and surely not too difficult to confirm, they were rather summarily rejected by the great majority of contemporary physicians,

¹⁹⁰⁴ HOWE A. C. *ibid* 51: 220, 1942

¹⁹⁴⁶ WOODWARD F. D. *Arch Otolaryng* 24: 723, 1936

¹⁹⁴⁷ SOLIS-COHEN M. *ibid* 30: 623, 1942

and it was not until a generation later that the Bostock-Blackley doctrine found a new champion in Dunbar (1903). He confirmed the observations reported by Elliotson and Blackley with regard to the significance of the pollens of grasses, and attempted to establish the therapy of the disease on a scientific basis. Regrettably, he made the mistake of assuming that the pollen albumin possessed a toxic property, instead of properly regarding the pollen albumin itself as the causative agent in hay fever. In accordance with this viewpoint, Dunbar attempted, by means of injecting animals with the presumptive "tovalbumin," to derive an antigenic serum—the so-called "pollantin"—with which to immunize patients passively. Weichardt's "grammol" was based on a similar principle: he attempted to achieve passive immunization by administration of serum taken from cattle fed on blooming grasses. This concept of intoxication caused by a specific pollen toxin again threatened to divert the line of investigation from the true doctrine of pollen allergy. Fortunately, however, the ideas of von Pirquet had already begun to attract attention; and under the influence of these, Wolff-Eisner (1906) and Weichardt (1907) came to regard hay fever as a special instance of human hypersensitivity to foreign protein (pollen protein), and thus to recognize hay fever as one of the allergic diseases. In this manner, the road leading to hyposensitization therapy was at last opened.

According to the now almost completely forgotten experimental work of Curtis (1900), it was found possible to achieve hyposensitization by means of subcutaneous injections of extracts of certain blossoms or pollens. This therapeutic approach was first systematically exploited by the English investigators Noon and Freeman in 1911. But it was Cooke, M. Walzer, Rackemann, and others who, in extensive and painstakingly performed experiments, perfected the preseasonal injection treatment—a method that was, until quite recently, considered the therapy of choice. The elaboration of coseasonal and perennial technics of parenteral therapy has added greatly to our armamentarium. Finally, within the past few years numerous attempts have been made to perfect an oral treatment method, involving the use of pollen or pollen digests

(pollen propeptans) and noteworthy results have been reported. Thus, Urbach, Jaggard, and Crisman²⁷ were able to protect guinea pigs highly sensitized to ragweed or timothy pollen against anaphylactic shock from inhalation of the respective pollen by oral preadministration of the appropriate pollen propeptans (for details, see p. 553).

2. NOMENCLATURE

Ever since it was duly recognized that the etiology of the disease under consideration consisted essentially in hypersensitivity to the pollens of weeds, grasses, trees, and bushes, and occasionally to the scents of certain plants, repeated attempts have been made to replace the hitherto commonly used designations with pathogenetically appropriate ones. The terms hay fever and hay asthma are misleading, since the manifestations are elicited not by hay itself, but by the pollens of the plants. The expression "hay fever" is further not warranted objectively, for it is only very rarely that the patient presents fever, properly speaking, although he not uncommonly does complain of a sensation of feverishness. The senior author once suggested the Latin terms *rhinopathia pollinosa* and *asthma pollinosum*; but we realize that these terms do not properly apply to all cases, for, as mentioned above, the same clinical picture can also be evoked by the scents of blossoms. The same criticism applies to the terms suggested by Kaemmerer and by Gutmann—*pollinosis* and *pollen allergy*. Terms such as rose cold and peach cold are today of little more than historical interest, although a rare case may, in fact, be due to the aroma of roses or other blossoms. Terms such as June cold, summer catarrh, and autumnal catarrh are too loose. Even the term seasonal allergic coryza—intended to differentiate between the seasonal and the perennial forms—is not an adequate designation, because there are seasonal coryzas other than hay fever, due to the ingestion of seasonal foods, to seasonal occupational exposures, as in threshing of grain or sorting of citrus fruits, or to seasonal air-borne mold spores.

Therefore, since it is apparently impossible to find a new, generally satisfactory designation for the disease, and since the term hay fever has long been in common use among physicians

as well as laymen it may be best to retain this like many another historic medical term—always bearing in mind however that practically all such cases are actually instances of pollen allergy

3. ETIOLOGY

The overwhelming majority of all cases of hay fever are attributable to the pollens of weeds, grasses bushes, trees and less commonly of flowers. A few cases are due to the scents of linden blossoms pseudacacia lilac elder, jasmine and roses. Lastly it should always be borne in mind that aside from the principal allergens—i.e. the pollens—associated (secondary) allergens are capable of playing an important and as yet inadequately recognized role in the maintenance of hay fever

a) POLLEN

A complete discussion of the morphologic, physical, chemical, and allergenic characteristics of pollen, as well as a discussion of the plants that are important in hay fever, has been presented in Part Two (p. 246)

The fact that pollens are to be regarded as the cause of hay fever has been proved in a number of ways. Most strikingly conclusive is probably the fact that the clinical picture can regularly be evoked, even outside of the hay fever season, by the mere application (nasal or conjunctival) of minute quantities of pollen. Passive transfer of the hypersensitivity by means of serum from a hay fever patient has been found to succeed in almost all instances (Grove and Coca,⁴⁶⁶ De Besche,¹⁹¹³ Urbach⁹⁷⁹ and others), and this is true both of the Prausnitz Kuestner procedure applied to human beings and of the Schultz Dale method applied to animals. Loveless⁶¹ transferred hypersensitivity to ragweed pollen by transfusions of the blood of allergic donors to normal individuals.

A number of authors have succeeded in rendering animals anaphylactic to pollen by the intraperitoneal or subcutaneous route (Alexander,¹⁸⁴⁹ Parker,¹⁰³ Harrison and Armstrong¹⁹⁵⁰ Walzer and Grove³³⁹ Ramsdell,¹⁹⁵¹

Caulfield Cohen and Eadie⁹⁹ F. Loeb¹⁹⁰⁷ Black⁹³³ Harrison¹⁹⁵³ Bernstein⁹⁵⁴ Urbach and Wolfram⁹¹⁹ and Coulson and Stevens^{1950a}). Ulrich⁹⁹ elicited local nasal reactions resembling hay fever by insufflation of pollen into nostrils of animals. Urbach Jaggard and Crisman⁷⁰ were the first to reproduce the conditions encountered in human beings since they were able to sensitize guinea pigs by the bronchial route and to elicit pollen asthma by re-exposing the animals to bronchial pollen inhalation. This method will undoubtedly form the basis for extensive study of the nature of pollen asthma and provide a tool for investigation of therapeutic measures against pollinosis in man.

Brunsting and Bailey were able to produce eczematous reactions in animals by topical application of ragweed pollen after an incubation period of from ten to fourteen days. By means of intra-abdominal injections of pollen in rabbits Winklerwerder and his associates⁶¹ were able to induce production of antibodies that were precipitating complement fixing and capable of sensitizing the human skin. By employing a lanolin like substance and paraffin oil containing killed tubercle bacilli as adjuvants with ragweed pollen extract Kulka and Hirsch¹⁹⁰⁵ produced sensitization and the formation of antibodies (including passively transferable antibodies) against the pollen to a far greater extent than with pollen extract alone. The sensitization was noted earlier than the presence of circulating antibodies.

Lastly the presence of specific antibodies can be demonstrated in the serum of hay fever patients both in and out of the season (Hensel and Sheldon¹⁹⁵⁷), by complement fixation with specific allergens. Employing the method of serum dilution, Levine and Coca¹⁹⁵⁸ demonstrated that during the course of treatment, the patient's serum often shows an increase in skin sensitizing antibodies. Schmidt and Lippard¹⁹⁵⁹ observed that after the patients re-

⁹⁰⁸ LOEB F. F. *Klin. Wchnschr.* 7: 803 1928

¹⁹⁰⁷ HARRISON W. T. *Pub. Health Rep.* 49: 462 1934

¹⁰³⁴ BERNSTEIN C. Jr. *J. Exper. Med.* 61: 149 1935

¹⁰⁰⁵ COULSON E. J. and STEVENS H. *Proc. Soc. Exper. Biol. & Med.* 45: 98 1940

⁹⁰⁸ KULKA A. M. and HIRSCH D. *J. Immunol.* 50: 127 1945

¹¹ HENSEL M. E. and SHELDON J. M. *J. Lab. & Clin. Med.* 26: 1886 1941

¹⁹⁰⁵ LEVINE P. and COCA A. F. *J. Immunol.* 11: 449 1926

⁹⁰⁵ SCHMIDT W. M. and LIPPARD V. W. *Am. J. Dis. Child.* 56: 550 1938

¹⁹¹³ BESCHE A. DE KLU. *Wchnschr.* 7: 1425 1928

¹⁸⁴⁹ ALEXANDER M. E. *J. Immunol.* 8: 457 1923

¹⁸⁴⁹ HARRISON W. T. and ARMSTRONG C. *Pub. Health Rep.* 39: 1261 1924

¹⁹⁵¹ RAMSDALL S. G. *J. Immunol.* 12: 231 1926

ceived hypodermic treatment, their serum acquired the capacity of neutralizing greater amounts of antigen. A similar increase in antibodies was found to occur in the serum of patients treated with ragweed pollen orally (Levin and Shulsky¹⁹⁶⁰). Cooke, Barnard, Hebal, and Stull¹⁹³⁷ observed that transfusions from parenterally treated hay fever patients to untreated hay fever patients at the height of their disease sometimes produced striking results. These were attributed to the probable presence of a transferable protective substance which Cooke later called the blocking or inhibiting antibody.

b) ODOR OF BLOSSOMS

Not infrequently patients are seen whose hay fever symptoms appear when they are in the vicinity of roses (*Rosa*), locust trees (*Robinia pseudacacia*), linden trees (*Tilia*), mock orange (*Philadelphus coronarius*), carnations (*Dianthus caryophyllus*), privet (*Ligustrum*), lilies (*Lilium*), common elder (*Sambucus nigra*), lilac (*Syringa vulgaris*), lily of the valley (*Convallaria majalis*), violet (*Viola*), and other odoriferous blossoms.

Sticker¹⁹⁶¹ quotes several medieval physicians to whom it was well known that roses and their fragrance can cause sneezing and rhinorrhea in some people. Sticker as well as Mackenzie¹⁹⁶² observed cases in which nothing but the odor of these flowers could have been the etiologic agent. Mackenzie¹⁹⁶² reported the case of a young woman in whom nasal congestion and a watery discharge were produced when she pinned a rosebud on her lapel; another case involved a patient who was subject to attacks of sneezing when only a single rose was placed in a very large room. Not only fresh flowers but even dry petals and essence of rose elicited the same symptoms.

In all the literature about the so-called rose cold or lilac cold, only Sticker,¹⁹⁶¹ Feinberg and Aries,¹⁹⁵⁴ Biederman,¹⁹⁵³ and the senior author¹⁹⁵⁴ have offered experimental evidence to show that volatile agents rather than pollen

may be the cause of allergic symptoms in some cases.

The assumption of pollen etiology in rhinorrhea can be excluded (1) if the blossoms in question have no stamens (and thus no pollen), since their stamens are transformed into petals—this is true of many grafted garden roses and lilacs; (2) if, as in *Robinia*, the peculiar position of the stamens, surrounded by a carina, makes it impossible for the pollen to be carried off by the wind; and (3) if insufflation of the particular pollen into the nostril of the patient elicits no symptoms.

Clinical evidence of the fact that odors or ethereal oils and not pollens are operative in such cases has been offered by the senior author¹⁹⁵⁸ in several ways. If, for instance, nasal and cutaneous tests with jasmine pollen are negative, although the patient maintains that his attacks invariably occur when he encounters jasmine, we utilize the following test. At a time when the patient is free of symptoms, a bunch of jasmine, covered with several layers of very fine organdy, is taken into his room during his absence. He is not permitted to enter until half an hour has passed, so that any pollen that may have been disseminated can settle down. If any symptoms are elicited under these circumstances, it is proved that they were caused by the odor only, that is, by the ethereal oils of the flowers in question.

Outside of the season, when fresh material is not available, it is rather difficult to perform direct odor tests. However, dried linden or pseudacacia flowers can be extracted in a well-closed container from which the volatile ethereal oils cannot escape. The odor tests can then be administered with this extract. Another method was employed by the senior author in the case of a woman who during a vacation in the mountains experienced attacks that she traced to the odor of a vast pine forest. The patient, who was continuously free of symptoms at home in Philadelphia, developed asthma in that city on using pine needle extract in her bath, or on washing herself with pine soap.

It should be stated here that patients who are hypersensitive to the smell of roses, for example, but not to the pollen of these flowers, frequently show hypersensitivity to other pollens, for instance those of grasses.

¹⁹⁶⁰ LEVIN, S. J., and SHULSKY, L. *J. Allergy* 13: 1, 1951.

¹⁹⁶¹ STICKER, G. *Das Heu- und verwaute Störungen*. Vienna: Holder, 1952.

¹⁹⁶² MACKENZIE, M. *Hay Fever, Its Etiology and Treatment*, with an Appendix on Rose Cold. London: Churchill, 1955.

¹⁹⁵⁴ BIEDERMAN, J. B. *Laryngoscope* 47: 825, 1937.

c) ASSOCIATED ALLERGENS

The substances most commonly acting as metallergens in hay fever are house dust, orris root, epithelial products (e g., animal hair and animal dander), materials used for stuffing mattresses and upholstery, molds, rusts, smuts, and certain foods, or, more precisely, the animal and vegetable proteins in these foods. All of them act according to the principles of metallergy (see p. 28). This is understood to mean that in a specifically allergized patient—in the condition under consideration here, sensitized to pollen—allergens other than the specific one can also elicit specific reactions, that is, symptoms of hay fever. Such allergens are referred to as metallergens.

The action of metallergens must be suspected in a case of hay fever when, despite every precaution against contact with the pollen (e g., in a closed room), the patient suddenly presents nasal, conjunctival, or asthmatic manifestations, or when a patient whose hay fever symptoms have shown considerable improvement or have even completely disappeared, suddenly manifests a recurrence of severe symptoms, although the pollinating season of the allergenic grass or weed is entirely over. It will surely not be necessary to stress the importance of these associated allergens, obviously, failure to consider or to recognize the existence of a polyvalent allergy will often make it impossible to prevent the recurrence of clinical manifestations despite specific treatment, and may, indeed, represent the reason for failure of strictly specific therapeutic measures.

Moreover, it must be remembered that the so-called associated allergens are also capable of eliciting other types of allergic manifestations (e g., gastrointestinal symptoms or cutaneous manifestations), in which case the present writers, in agreement with Moro, use the term *parallergy* rather than metallergy. (More explicitly, *parallergy* is understood to refer to a state in which a specifically sensitized organism reacts to other types of allergens with manifestations clinically unlike those evoked by the first allergen.)

Needless to say, we are here concerned with associated allergens only in so far as they have an effect during the hay fever season, and not

with those that elicit symptoms at other times of the year.

The most important group of associated allergens is composed of the various types of dust: house dust, book dust, flour dust, and face and body powders particularly those containing orris root. House dust must be borne in mind in cases in which the patient sleeping in a room with the windows closed at night, has attacks of sneezing, flour dust may be suspected in housewives, cooks, and persons residing over a bakery, and face powder must be considered in women, of course, but also in men when the patients have hay fever manifestations while in a theater, for example.

Other important associated allergens are animal epithelial substances, as well as animal emanations. Thus, Piness and Miller¹⁰⁴ have demonstrated hypersensitiveness to animal hair and wool in a large number of cases, Gutmann, to feathers in bedding, Parlato,¹⁰¹ to the hairs and scales of moths and butter flies, during the season when relatively large amounts of these insect products are carried in the air. Kragh reported a hay fever patient who presented symptoms when he was in the proximity of horses during the season, as well as on exposure to pollens. All these authors have advanced conclusive proof—either by means of positive skin tests, or by positive conjunctival and nasal tests—of the allergenic nature of the substances mentioned. During the hay fever season, the patient not uncommonly manifests hypersensitiveness to the usually nonallergenic pollen of decorative flowers, and also to pyrethrum, which consists of finely pulverized chrysanthemum pollen.

Another group requiring consideration is that of the foodstuffs. For the purposes of this discussion, we must immediately eliminate those food items that may contain pollen or species-specific proteins, and that may thus elicit hay fever by way of the gastrointestinal route. The former factor was operative, for example, in a case mentioned by Funck that was caused by honey, which notoriously contains quantities of completely unaltered pollen. The latter factor is in question when, as reported by Benjamins and Gutmann, a rye pollen sensitive patient presents symptoms fol-

¹⁰⁴ PINESS, G. and MILLER, H. *California & West Med.* 23: 1014, 1925.

lowing ingestion of rye bread. These manifestations failed to appear so long as rye bread was excluded from the diet, only to reappear when this bread was again eaten. The senior author has made similar observations—namely, following ingestion of corn by an individual hypersensitive to corn pollen, and following drinking of jasmine-flavored tea by an individual hypersensitive to the odor of jasmine. However, there are those observations according to which vegetable foods, botanically in no way related to grains and grasses, as well as certain animal products, elicit nasal, conjunctival, and even asthmatic manifestations during the hay fever season. Thus, Cohen and Rudolph,¹⁹⁶⁵ Rowe,³¹⁰ Gelfand,¹⁹⁶⁶ Whitfield, Eskuchen, Gutmann, and others have reported pertinent instances of symptoms following ingestion of onions, gooseberries and other fruit, certain kinds of wine and beer, chocolate, meat, eggs, etc. A possible explanation might be that, as a consequence of an allergic pollen enteritis, larger amounts of food protein may be absorbed during the hay fever season.

Moreover, drugs, particularly acetylsalicylic acid, may also act in this manner.

As to molds, rusts, and smuts, these are capable of acting as metantigens or as independent antigens (for further details, see p. 283). Patients allergic to both grasses and ragweed, who continue to manifest symptoms between the two seasons, are especially likely to be hypersensitive to *Alternaria* or other fungus spores. In occasional instances, one also encounters a metaspecific hypersensitiveness to the drugs used in the symptomatic treatment of the case, such as ephedrine or cocaine, as well as to the menthol added to various nasal preparations; sometimes the emulsion base of a nasal jelly is similarly not tolerated. Lastly, bacteria from infected sinuses may act as associated antigens in a great many cases.

It should be noted that metallurgy is not to be confused with the state that we prefer to call pathergy and that accounts for the well-known fact that, during the pollination season, hay fever patients become nonspecifically sensitive and respond with attacks of sneezing, lacrimation, or asthma to all types of irritants,

such as sunlight, perfumes, automobile exhaust gases, naphthalene, camphor, insecticides, constituents of commercial fertilizers, and fluctuations in temperature. However, one need not pay any special attention to these nonspecifically irritating factors, for they lose their effect just as soon as the underlying hypersensitiveness to pollen is controlled. The differentiation between associated allergens and mere nonspecific irritants can almost always be achieved by means of close clinical observation, supported by appropriate elimination and re-exposure tests, and sometimes by skin tests.

4 PATHOGENESIS

In hay fever—as in all other allergic diseases—one must endeavor not only to establish the identity of the eliciting allergen (pollen, blossom scent, associated allergen), but also, whenever possible, to discover the factors predisposing to allergization. The success or failure of therapy may very well depend on the recognition and appropriate management of the predisposing factors or contributing causes. Outstanding among these are the so-called “factors of civilization,” as well as heredity, exposure, and climate.

It should be stated, first of all, that hay fever is definitely a disease of civilization. This is perhaps best brought out by the fact that, according to Scheppegegrell,³⁵⁷ there were some 1,200,000 hay fever patients in the United States in 1922, while the present figure is conservatively estimated to be somewhere between 4,000,000 and 5,000,000—3 per cent of the entire population (Piness and Miller³⁴⁸). Other surveys arrive at even higher figures, such as 8 per cent (Pipes³⁴⁶) and 10 per cent (Service³⁴⁷). According to Sticker,¹⁹⁶¹ there were only a few hundred persons afflicted with hay fever in the large cities of Germany at the turn of the century, whereas in 1928 more than 1 per cent of the urban population of Germany—i.e., some 600,000 persons—were regarded as suffering from hay fever (Hansen¹⁹⁶⁷). This striking increase cannot be entirely due to the fact that the physician of today is able to recognize the disease picture of hay fever more accurately and more promptly; the rapid rise in incidence must be attributed to other causes—external as well as internal. Most important

¹⁹⁶⁵ COHEN, M. B., and RUDOLPH, J. A. *Arch. Int. Med.* 45, 742, 1930.

¹⁹⁶⁶ GELFAND, H. H.; *Am. J. Med. Sci.* 152, 81, 1933.

¹⁹⁶⁷ HANSEN, K. *Deutsche med. Wchnschr.* 54, 1447, 1928.

of these are the factors of exposure brought about by the conditions of modern civilization irritation of the mucosa by automobile exhaust fumes by the smoke from chimneys locomotives and steamships by gases from factories and by the increase of the dust content of the air as a result of heavy city traffic Another noteworthy factor is the way in which urban areas are planted with parks within the city proper and a belt of fields and meadows surrounding the closely built up zones Further more a very important part is played by the tension and emotional strain of city life in general All this serves to explain why the urban population shows a definite predilection for the disease

On the other hand it has never been possible to establish such a thing as a racial predisposition, for although the Japanese Koreans and other racial groups are practically never afflicted with hay fever at home they contract the disease in America in the same percentage as do native white Americans (Hara³⁶⁸) this would certainly seem to indicate that external factors are decisive in this connection It has often been claimed that Jews show a racial tendency to the disease—and it is true that the incidence of hay fever among Jews is very high—but this according to Rehsteiner³⁶⁹ is merely another example of class predisposition

According to Cooke Bray and others heredity is the most important predisposing factor However all authorities agree that it is not the hypersensitiveness of certain organs or to certain substances that is inherited but rather the capacity for or the tendency to allergization Nevertheless it cannot be denied that hay fever more than other allergic conditions shows a very high familial incidence

Third in importance in the writers opinion is the factor of exposure—that is to say massive contact with antigens or in other words with large quantities of pollen This explains why so many patients are able to trace the onset of their symptoms back to a ride by train or automobile through fields and meadows in blossom to proximity to the mowing of hay, to games in a hayloft or to a long march

through fields of grain in bloom as in military maneuvers Thus allergization is the result not so much of regular daily repeated exposure to the allergen as of the occasional intermittent influence on the organism of contact that sometimes need not be massive (Doerr) This fact based on countless observations serves to explain the apparently paradoxical distribution of hay fever in urban and rural districts Thus the comparative figures for Switzerland according to Rehsteiner³⁶⁹ are 0.8 per cent and 0.13 per cent respectively This author's finding that among Swiss students coming from rural districts to urban high schools the incidence of hay fever rises from 0.13 per cent to 1.5 per cent would also indicate the effect of irregular exposure and of fluctuating intensity of contact with the given pollen Another especially pertinent example is to be found in the report of Dutton³⁷⁴ that in 1937 many farmers and other inhabitants of the Mesilla valley in New Mexico and Texas acquired hay fever from sugar beet pollen and beet seeds following especially intensive planting of beetroot in that district during 1936

Haag³⁷⁰ made a special study of meteorologic influences in hay fever particularly with regard to the effects of fluctuations in barometric pressure In a series of experiments on guinea pigs he demonstrated that in dealing with highly sensitized animals the results of a reinjection of pollen were to a considerable extent dependent upon the atmospheric pressure when the barometer was rising the reactions were almost completely inhibited whereas when the barometer was falling the response was severe and usually fatal The influence of meteorologic conditions as represented by fluctuations in barometric pressure was thus experimentally proved Hansen and Michenfelder had previously called attention to the fact that the reactions to allergy testing in human beings are greater when the barometer is low than when it is high

In rare instances the patient's psychic state may also serve as a predisposing factor Several examples will serve to illustrate this point Schultz reported the case of a mother anxiously waiting in the garden outside a hospital while her child was undergoing an operation it so happened that certain plants

³⁶⁸ HARA H Arch Oto-aryng 20: 658 1934

³⁶⁹ REHSTEINER S hacz Bl f Gsadi tschl 1926

³⁷⁰ HAAG F E Klin Wchns hr 11: 1228 1932 12: 1091 1933

were blooming in the garden at the time, and the patient was hypersensitive to these blossoms from that time on. The famous French clinician, Trousseau, suffered his first attacks of hay fever and asthma after having spent some time in his hayloft, where he was personally supervising the weighing of oats, since he could no longer trust his coachman. Trousseau himself attributed the onset of these symptoms of hypersensitiveness, which he had never previously suffered, to the fact that he was under severe nervous strain at the time because of his servant's dishonesty. Strebel described the case of a farmer who suffered his first attack of hay fever after having been severely frightened.

The psychologic factor probably exerts its influence, first, by lowering the threshold of excitability to the allergen, and later, without intervention of the allergen, by means of a conditioned reflex. This may serve to explain the fact that hay fever patients may also suffer attacks when—as in Mackenzie's case—they see paper flowers (e.g., roses) that are such good imitations that they believe them to be real. The senior author has seen a patient who invariably suffered attacks of sneezing while witnessing the garden scene of the opera *Faust*.

The rôle of infections as a predisposing factor is far less important in hay fever and pollen asthma than it is, for example, in other forms of asthma. Occasionally, the patient's history reveals that the first nasal or bronchial manifestations followed a cold, grippé, or other acute infection. In cases of this kind, the lowered resistance of the mucosa resulting from the infection may well pave the way for allergization by pollen.

As regards the influence of trauma, it cannot be denied that nasal or tonsillar operations not infrequently seem to be predisposing factors. Therefore, allergic individuals—adults as well as children—should not undergo such operations during the hay fever season.

In addition to the predisposing influences, there are a number of contributory factors of importance in hay fever, particularly weather and climate. The following atmospheric or meteorologic conditions have an especially unfavorable influence in hay fever: (1) low humidity of the air during long periods of fair weather; (2) winds coming from areas of fair

weather—thus, the sky may be cloudy over the district in which the observations are being made, but so long as the air is not moistened by rain or fog, the prevailing wind may very well carry pollen from other districts, and this may serve to explain the severe attacks of hay fever occasionally observed during cloudy weather; (3) sudden changes in the direction of the wind, which can carry pollen from various directions, and thus increase the total supply in the air over one area. Aside from wind, the factors of heat and humidity exert a strong influence on hay fever patients by stimulating the production of pollen. Charts show that the clinical symptoms and the curve of atmospheric pollen content run contrary to that of atmospheric humidity—for under conditions of low humidity and high temperature, the air contains a maximal amount of pollen. On the other hand, a long rainy spell clears the air of pollen, partly by inhibiting the shedding of pollen and partly by precipitating the pollen already in the air.

In a discussion of the pathogenesis of hay fever, consideration must be given to several other points—general as well as special—that have a bearing on the clinical manifestations.

The date on which the annual hay fever attack begins is subject to considerable variation, depending upon the individual patient, meteorologic conditions, and geographic location.

The degree of hypersensitiveness to pollen may fluctuate to a certain extent from time to time in a given individual, regardless of the amount of pollen to which he is exposed. The present state of our knowledge does not enable us to say to what extent these variations may be due to the influence of unrelated factors (e.g., functional disturbances of the endocrine glands, such as hyperthyroidism or pregnancy) that may well have an effect on the individual's relative degree of reactivity.

The fact that the severity of hay fever varies from year to year is attributable almost exclusively to external meteorologic factors that have a direct influence on the amount of pollen produced by the plants. The most unfavorable combination is: (1) damp weather prior to the season, promoting the growth of grasses or weeds; (2) dry sunny weather during the hay fever season, furthering the full develop-

ment of the blossoms and (3) moderate to strong winds which carry the pollen long distances. The frequently observed daily and even hourly variations in the severity of hay fever manifestations also depend on the weather rainfall temperature and wind direction and force. Almost all hay fever patients suffer their most severe attacks in the morning; this is due to the fact that most plants shed their pollen early in the morning shortly after sunrise.

At this point it might be appropriate to mention certain observations concerning the capacity of the human nasal secretions and blood to break down pollen. Insufflation of plant pollen into the nostrils of a healthy individual will as Gutmann²⁴ has shown evoke either no response whatever or at most a brief sneezing spell. Microscopic examination of the secretion following such sneezing reveals the plant pollen present in the nasal mucus intact and completely unaltered as regards the hard exines. In hay fever patients however the grains of the pollen to which the individual is hypersensitive are found to be changed and indeed partly ruptured and partly germinated. One must conclude therefore that the nasal mucous membrane or mucus contains a substance—possibly an enzyme—that can break down the pollen. Probably closely related to this phenomenon is the demonstration by Cahn Bronner²⁵ that the nasal discharges of hay fever patients shows a high content of lysozyme as compared with healthy subjects. This enzyme found in normal nasal secretions and diminished or absent during the first days of a common cold is capable of clearing a suspension of a *Sarcina*. *Micrococcus lysodeikticus* first by adsorption to the bacterial surface and then by dissolution of the bacterial cell. Gutmann has also demonstrated that various plant pollen extracts are best made in a very special menstruum the most suitable being in a given instance the one that corresponds most closely to the pH of the patient's nasal secretions.

This capacity of the nasal mucus of hay fever patients to disrupt pollens is confirmed by the results of another experimental procedure of Gutmann's namely the finding that posi-

tive skin reactions are elicited by injection of the sterilized nasal secretions sneezed by a hay fever patient; no cutaneous reactions are observed however following injection of the nasal secretions from a healthy individual's sneeze in response to insufflation of pollen into the nostrils.

On the other hand according to Harley²⁷ the blood of hay fever patients has the opposite effect on pollen while blood from normal individuals has a strong tendency to dissolve the pollen grains blood from hay fever patients has scarcely any such effect.

5 PATHOLOGY

Pollinosis involves chiefly the conjunctiva and the mucous membranes of the nose and bronchi. There is no difference in pathology as between the nasal bronchial and conjunctival allergic inflammations whether caused by pollen or other external allergens. The gross and microscopic changes are fully discussed in the sections on rhinopathy and asthma and in the chapter on eye diseases.

However the outstanding clinical pathologic feature is the presence of large numbers of eosinophils in the nasal secretions. This particular finding has some usefulness in diagnosis. It is treated in detail on page 49*.

6 SYMPTOMATOLOGY

One of the characteristics of hay fever is the fact that the patient is affected each year with the same symptoms at the same time (at the pollination time of trees grasses weeds or bushes according to the case).

The disease usually begins with repeated attacks of nasal irritation and sneezing sometimes accompanied by conjunctivitis and bronchitis. The symptoms appear at the start of the blooming season of the plant involved. The first attacks are often so mild that they are not recognized by the inexperienced patient as hay fever manifestations even the physician may hesitate to give a definite diagnosis of hay fever. When such symptoms of mucous membrane irritation are observed in young children the diagnosis can sometimes be reached only with the aid of a history that one or both of the parents are afflicted with hay fever or other allergic dis-

* CAHN BRONNER: C. E. Ann. Oto. Rhin. & Laryng., 51: 250, 1942.

* HARLEY: D. B. & M. J. 1: 138, 1933.

ease. Otherwise, the true nature of the condition is not infrequently unrecognized during the first season, and the diagnosis of hay fever is made only in the following year, when the conjunctival and nasal symptoms reappear at the blooming time of the given grasses or weeds without any previous "cold."

Regarding the onset of symptoms, one must distinguish between various types. There are patients in whom the disease manifests itself not by sudden acute attacks, but slowly and gradually; in such cases, forerunners of the actual symptoms are noticeable two or three days—sometimes even a whole week—beforehand. The patient feels weak and depressed, complains of headaches and irritability, sometimes of drowsiness after meals, uneasiness, digestive sluggishness, and finally of vague disturbances in the eyes, nose, and ears, particularly after having been out in the open. All these symptoms are characteristic of the stage preceding the actual attack.

In most instances, however, the symptoms develop within a few hours and surprise the patient with their severity. Here we must distinguish between two forms: first, that in which the conjunctival manifestations dominate the picture at the beginning of the attack, and, second, the cases in which the nasal symptoms are particularly distressing. Almost all patients, however, manifest both conjunctival and nasal symptoms within a few days, whereas asthmatic symptoms do not appear for two or three weeks, and then only in a minority of cases. The hyperemia of the bulbar and the palpebral conjunctiva occasionally produces chemosis, with more or less marked edema of the eyelids.

In the majority of cases, the picture is dominated, at first, by nasal manifestations. Along with tickling, burning, or itching sensations in the nose or soft palate and even the gums, the patient experiences a distressing urge to sneeze. This is soon followed by sneezing, which affords some relief, and in the course of which quantities of a clear watery secretion are expelled. Shortly thereafter, there are paroxysms in which the patient sneezes explosively from ten to twenty and sometimes even as many as fifty times in succession, until he is completely exhausted and bathed in sweat; moreover, there is occasionally

severe pain in the thoracic muscles and diaphragm. In severe cases, the patient is completely incapacitated and cannot even take nourishment, he is obliged to lie down and rest in a closed and darkened room. It is by no means rare for a patient to use dozens of handkerchiefs in the course of such an attack.

The secretions of the nasal and conjunctival mucosae are, at first, clear and watery, and contain very few cells. Later, they become thicker, owing to mucus and in part to the presence of eosinophile cells and Charcot crystals.

At this stage, the patient's sense of smell is heightened to a pathologic degree: he finds odoriferous flowers, perfumes, and other aromatic substances particularly distressing.

The ophthalmic symptoms of hay fever are characterized by one or more of the following, depending on the severity of the case: itching, a "sandy" sensation of the lids, redness and injection of the palpebral and bulbar conjunctivae, lachrimation, and photophobia. In extreme cases keratitis may occur, the ulcers being marginal, and situated about 1 to 2 mm. from the limbus. At first they are discrete and involve just one quadrant, later they may become large, coalesce, and even involve the entire perimetry of the cornea (Blank and Levitt³¹). Iritis, uveitis, and retinitis have been reported.

Moreover, these nasal and conjunctival manifestations are frequently accompanied by "sinus headaches," a feeling of heaviness in the head, a marked degree of photophobia, and mental depression.

Then, after a variable length of time, and chiefly as a result of the necessity of breathing through the mouth, the irritation of the mucous membranes spreads to the pharynx, the hard palate, and the upper respiratory passages, causing dryness, "burning," and a distressing desire to swallow. A dry, irritative cough may develop as a result of pharyngeal irritation and also because of the marked nasal obstruction. Patients occasionally complain of earaches. Dyspnea of a strictly expiratory character may appear, in part as a continuation of the process with inflammation of the pharynx and the lower respiratory passages. In rather rare cases, however, wheezing may appear without concomitant nasal or con-

junctival symptoms making the diagnosis quite difficult. Pollen asthma is by no means uncommon. Thommen¹⁹ encountered it in one third of all his hay fever patients. Vaughan²¹ in about 35 per cent and the present writers in about 29 per cent.

The asthma usually appears after the patient has had hay fever for several years; at first it is seen in association with the other manifestations and toward the latter half of the season but later it often remains as the sole symptom recurring each year with increasing severity. The great danger in cases of asthma due to pollen is that although the

connection it should be mentioned that according to Rinkel¹⁹⁷ hay fever with abundant rhinorrhea and without itching is characteristic of a concomitant food allergy.

While the patient has his hay fever he not uncommonly complains of a sensation of feverish warmth especially in the hands and feet and sometimes of waves of heat over his whole body. During these spells his temperature need not be appreciably increased; however one sometimes finds the temperature to be from 1 to 2 degrees Fahrenheit (0.5 to 1 degree Centigrade) higher than on normal days. Occasionally the temperature may



HAY FEVER WITH ANGIONEUROTIC EDEMA

FIG. 246 Note swelling of face, narrowing of palpebral fissures and conjunctivitis following nasal insufflation of chestnut pollen.

manifestations appear only during the pollinating season for the first few years the condition can in time become nonspecific so that it will appear at any time of the year.

It should however be noted—as Vaughan²¹ has pointed out and as has been confirmed by the present writers among others—that asthma that appears only during the hay fever season is sometimes due not to pollen but to some other allergen. The patient may be allergic to some food; for example and elimination of this food item from the diet will prevent the appearance of asthmatic symptoms at any time of the year other than the hay fever season; however the patient is able to eat the same food with impunity. In this

FIG. 247 Absence of swelling and symptoms when pollen insufflation was preceded by orally administered specific pollen prophylaxis.

reach 100.4 F (38 C), 102.2 F (39 C) and as the writers themselves have seen 104 F (40 C) and even 105.8 F (41 C). The patient then presents pronounced systemic manifestations including enlargement of the spleen and extreme eosinophilia—symptoms that are likely to confuse the physician when the patient has his first such attack.

The senior author¹⁹⁷⁴ has had occasion to observe an attack of this kind in which the picture was further complicated by angioneurotic edema.

Early in the month of May a healthy man with a negative history suddenly and without apparent cause

¹⁹⁷ RINKEL, H. J. *J. Allergy* 7: 356, 1936.

¹⁹⁷⁴ URBACH, E. *Monatsschr.* 10: 534, 1931.

complained of sensations of itching and burning of the conjunctiva, and on the following day presented a chemosis conjunctivae. At the same time there was swelling of the nasal mucous membranes, and somewhat later, edema of the face, combined with marked malaise and a temperature of 102 F (38.9 C). The spleen was palpable 1½ fingerbreadths below the costal margin and quite firm. The leucocyte count was 10,200 with 12.5 per cent of eosinophils. After forty-eight hours of rest in a completely closed room, the patient's temperature dropped and the swelling and conjunctivitis disappeared. Since it was known that the patient had been sitting under a blossoming horse-chestnut tree (*Aesculus hippocastanum*) the day he was taken ill, a few pollen grains were applied to his nasal mucous membrane, as a result the patient again presented marked swelling of the face (Figs. 246, 247), rhinitis conjunctivitis, and a fever reaching 100.8 F (38.2 C) together with a subjective feeling of malaise and a rise in eosinophilic leucocytes up to 19 per cent, at this time

allergic disease involving the entire organism, in the course of which a given case usually presents clinically manifest symptoms only in certain organs or tissues.

Regarding the cutaneous manifestations, hay fever patients occasionally present urticaria during the pollination season and at no other time. That this is an expression of a cutaneous allergy to pollen is confirmed by Sternberg's¹⁵² observations and experiments showing that preseasonal therapy will prevent the urticaria as well as the hay fever, but that these symptoms reappear the following season if no such measures are taken. The writers have seen extensive urticarial plaques on the faces, forearms, and hands (Fig. 248) of hay



FIG. 248 URTICARIA DUE TO MASSIVE CONTACT WITH GRASS POLLEN. Exposure occurred when patient rolled in grass during pollination season.

the spleen was again found to be enlarged and hard. After he had rested for twenty-four hours in a closed room, all the manifestations again retrogressed.

In addition to the principal symptoms of pollinosis—i.e., conjunctival, nasal, and bronchial—there are severe clinical manifestations that appear only rarely, and that may be diagnosed as due to pollen allergy only if they always appear during the course of the hay fever or at least during the hay fever season and end spontaneously with the cessation of pollination, or if they show improvement following effective therapy against the pollen allergy. When such symptoms (e.g. cutaneous, gastro-intestinal, or bladder), which will be described below, appear in place of the typical hay fever manifestations and only during the season, they are referred to as hay fever equivalents.

All this is evidence of the fact that pollinosis is not by any means a local disease of the upper respiratory passages, but a generalized

fever patients who had been lying on the blossoming grass in the early summer. Mention might also be made here of the swellings of the knee joints occasionally observed by Mohr and Sticker in association with hay fever attacks. Isolated reports point to the possibility of alternating affection of the skin and of the mucosa, Sticker¹⁵⁶ has particularly stressed this alternating involvement. However, instances of isolated pollen urticaria rarely occur—that is, cases in which only wheals appear during the pollination season, without accompanying nasal or conjunctival manifestations, but with positive cutaneous tests to pollen—a true hay fever equivalent (Taub and White¹⁵⁷).

The fact that the skins of hay fever patients present urticarial manifestations only at times may well be explained by the circumstance that massive contacts with pollen are infrequent

¹⁵² STERNBERG, L. *J. Allergy* 4: 336, 1933.

¹⁵⁷ TAUB, S. J., and WHITE, C. *Ibid.* 2: 186, 1931.

and then only brief. For, when an applicator soaked with a pollen solution is in close contact with the skin under the nose for some time, as in the course of nasal testing with liquid extracts, urticaria will frequently appear on the upper lip just below the nostrils. Moreover, one sometimes sees the development of urticaria apart from the specific reaction in the vicinity of sites of intra and subcutaneous injections of pollen. Lastly, generalized urticaria on the basis of an anaphylactic mechanism may follow administration of excessively large doses of pollen extracts in the course of



FIG 249 DERMATITIS DUE TO POLLEN RECURRING EVERY SUMMER DURING HAY FEVER SEASON

hyposensitization, or accidental entrance of the extracts into the blood stream.

When dermatitis appears during the hay fever season and persists despite appropriate therapy, the physician should consider the possibility of pollen dermatitis especially if the patient is suffering from hay fever as well. Pertinent observations were reported over a century ago by Elliotson: the regular appearance of 'eczema' on the hands of a hay fever patient when she carried bundles of grass. Brown, Milford, and Coca,¹⁴⁰² however, consider the pollen oil rather than the pollen protein to be the allergenic factor, and therefore recommend patch tests with the oily (lipoid) fraction of the pollen, in preference to intra cutaneous testing with the water soluble portion. Ragweed pollen appears to be particularly dangerous in this respect (Gay and

Ketron¹⁹⁷⁷ Pascher and Sulzberger¹⁹⁷⁸ Brunstung and Anderson¹⁴⁰⁰ Huber and Harsh¹⁹⁷⁹). But cocklebur (Rowe¹⁹⁸⁰) and other pollens can also call forth cutaneous eruptions. According to Cunningham and Wolfe¹⁹⁸¹ the fact that these skin conditions respond favorably to specific treatment constitutes additional proof of the pollen etiology of these dermatitides. FIGURE 249 illustrates one of the present authors' cases. Jordon, Campbell and Osborne¹⁴⁰³ observed 9 cases of ragweed dermatitis, chiefly on the exposed surfaces in patients employed in the flour and grain industries, and pointed out that this is a common industrial hazard among such workers. Patch tests were positive with pollen oil, as well as with alcoholic extracts of the weed and with a fresh leaf from the plant. Occasionally dermatitides are true hay fever equivalents (Wilmer¹⁹⁸²). Such a case was observed by Mitchell and Mitchell¹⁹⁸³ and was proved by patch test and the results of hyposensitization to be due to the albumin fraction of timothy pollen. Grass pollen oil produced no reaction. There is a noteworthy case of Cunningham's—a nursing infant that developed dermatitis following each injection of hay fever extract in the mother. When the injections were stopped the baby's skin disease cleared up, only to recur when treatment was resumed.

An interesting observation was reported by Hollander⁷⁷⁰. His patient presented a dermatitis of the penis only during the hay fever season. The allergen however, was not pollen, but ephedrine which the patient used in a nasal spray. When the penis was sprayed with a 2 per cent solution of ephedrine, an acute focal dermatitis was evoked, although a patch test on the arm was entirely negative. Discontinuance of the nasal spray led to permanent freedom from the penile eruption. Kahn¹⁹⁸⁴ and Davidson¹⁹⁸⁵ reported the appearance of an acneform dermatosis during the

¹⁹⁷⁷ GAY L N and KETRON L W. *ibid* 3: 478 1952

¹⁴⁰⁰ PASCHER F and SULZBERGER N B. *Arch Dermat & Syph* 28: 223 1933

⁷⁴ HUBER H L and HARSH G F. *J Allergy* 3: 578 1932

⁷⁵⁰ ROWE A H. *Arch Dermat & Syph* 39: 149 1939

¹⁴⁰¹ CUNNINGHAM T D and WOLFE A M. *J Allergy* 4: 48 1932

¹⁴⁰² WILMER H B. *M Clin North Amer* 13: 1047 1930

⁷⁶⁰ MITCHELL J H and MITCHELL W F. *J Allergy* 16: 48 1945

¹⁴⁰³ KAHN I S. *ibid* 10: 235 1939

¹⁴⁰⁴ DAVIDSON M T. discussion to Kahn¹⁹⁸⁴

grass pollen season or following nasal treatment with pollen extracts.

Moreover, pollen allergy can elicit specific reactions in a variety of organ systems, these reactions cannot, of course, be correctly interpreted unless the patient simultaneously presents typical hay fever symptoms, or unless the symptoms appear during the pollination time and disappear after avoidance of the specific agent. Sticker¹⁹⁶¹ described migraine attacks partly alternating and partly simultaneous with the nasal manifestations. Some cases have been observed in which the patients complained of marked dizziness and an increase in the flow of saliva, also of an increase in an existing difficulty in hearing. A few isolated reports tell of patients complaining of unusual precordial pain similar to those encountered in angina pectoris; examination of the heart has not yet revealed any organic changes in cases of this kind. Neurologic manifestations appear in the form of neuritides, but particularly as neuralgias of the supraorbital nerve, as well as of other branches of the trigeminal. There also occur, in the nerves of the extremities, manifestations that can sometimes assume the proportions of a bilateral sciatica. We are not referring here to cases of this kind that very occasionally follow injections of pollen extracts. Joint complaints of the nature of rheumatism are encountered relatively infrequently.

Gutmann¹⁹⁵⁶ reported cases of almost unmanageable nasal hemorrhage, and Joachimovitz¹⁹⁵⁷ described menstrual irregularities, such as metrorrhagia and menorrhagia, the latter can reach the degree of a severe genital hemorrhage; in a case reported by Adelsberger and Munter,¹⁹⁵⁸ it even led to a spontaneous abortion in the third month. It is uncertain, however, whether hemorrhages of this kind are to be regarded as a direct or indirect consequence of mucous membrane allergy. On the other hand, the occasionally observed vaginal discharge may well be regarded as specific, since it is high in eosinophile cell content (Joachimovitz¹⁹⁵⁷). Similar genital manifestations are occasionally observed as part of an ana-

phylactic reaction following excessively strong pollen injections (see p 550). H. L. Huber reported 3 children with pruritus vulvae during the ragweed pollinating season. The symptoms disappeared following treatment with pollen extract.

Involvement of the gastro-intestinal tract may be suspected if there is intestinal colic; the latter may also appear after overdosage of pollen extract and especially following oral pollen therapy. Intestinal disturbances occasionally act as hay fever equivalents. Explosive attacks of vomiting sometimes appear suddenly during the hay fever season; these attacks are followed by the most severe abdominal pain, which may be localized in certain sites, such as the epigastrium or the region of the gallbladder or of the appendix, and are occasionally accompanied by diarrhea. Such symptoms sometimes simulate duodenal ulcer, cholecystitis, or appendicitis so perfectly that operation is seriously considered. The manifestations can be rapidly controlled by means of epinephrine.

One of the senior author's patients, during especially severe hay fever attacks, would complain of a sort of ravenous hunger that could be appeased immediately by ingestion of bread or other food. This observation is of interest in view of Eiselsberg's claim¹⁹⁵⁹ that anaphylactic states occasionally lead to a very pronounced hypoglycemia.

Under normal circumstances, only the mucosa of the upper respiratory tract is exposed to contact with pollen. However, the fact that all the mucous membranes of a hay fever patient can, in principle, react allergically to such contact with pollen is shown by Prausnitz' experiment¹⁹²⁸; dusting of the anal mucosa of such patients with pollen elicits extremely severe pruritus with hyperemia. Rarely, the urinary passages are involved, with symptoms of urinary tenesmus and urgency.

With the exception of the severe neuritides, which represent a contraindication for specific treatment, all these hay fever symptoms are likely to respond favorably to hyposensitization or deallergization therapy.

At this point we might again call attention to the phenomenon of pronounced physical inadequacy and psychic depression during the

¹⁹⁵⁶ GUTMANN, M. J. et al. Die Pollenallergie. Manisch Gmelin, 1959.

¹⁹⁵⁷ JOACHIMOVITZ, R. Med Klin 28 294, 1926.

¹⁹⁵⁸ ADELSBERGER, L., and MUNTER, H. ibid 28 860, 1932.

¹⁹⁵⁹ EISELSBERG, K. P. Wien klin. Wchnsch. 53. 790, 1940.

hay fever season, in both child and adult patients. Thus Sternberg¹⁹¹⁰ described a 32 year old patient who became dull listless, confused, and totally incapacitated during the months of August and September for eleven consecutive years. No symptoms of hay fever or asthma were present. Skin testing with ragweed pollen was positive, and hyp sensitization resulted in marked improvement. At the same time the resistance to staphylococci and streptococci infections is apparently lowered. Moreover, there is a striking intolerance to alcohol. Lastly, while many patients have a distressing overexcitability of the olfactory sense, some complain of a state of anosmia.

Finally, mention must also be made here of the fact that concurrent disease conditions—in themselves in no way related to allergy—often undergo a change, usually for the worse, rarely for the better, during the hay fever season. This is true especially of gallbladder conditions and of gout, when they happen to be present along with hay fever.

Even more characteristic than the nature of the symptoms themselves is the course of hay fever. For it is almost directly dependent upon the patient's exposure to pollen, on the one hand, and the weather on the other. This explains why one often observes several sudden exacerbations and distinct remissions, of several hours' duration, all taking place in one day. Thus, in fair weather the patient is likely to suffer an attack every time he leaves the house, particularly if he should take a walk in the country, or even if he travels by train or automobile. As long as he remains in a closed or air conditioned room, the symptoms, if any, are likely to be mild. In rainy weather they tend to be slight or absent. However, it is occasionally observed that the symptoms do not improve even on cloudy days, this is usually due to the fact that the wind often carries great quantities of pollen from areas of fair weather.

The actual duration of symptoms in a given case can vary considerably, depending on the pollination season of the trees, grasses, or weeds responsible. But even after the local symptoms have retrogressed, there is a later phase

marked by the persistence for some time, of general weakness and heightened irritability, with a tendency to recurrences of sneezing spells or asthma.

Another frequent peculiarity of hay fever consists in the fact that, in the different periods of life, different organs show a greater predilection for the disease. During childhood, the eyes and nose and occasionally the skin as well, are affected, in addition to these localizations, youths are likely to show involvement of the pharynx and the bronchi, while in adults asthma is not rarely the outstanding factor.

One occasionally hears the claim that when the patient reaches an advanced age, the disease disappears spontaneously. This is a relatively rare occurrence, indeed, elderly patients do often present milder symptoms, but it must be said that this is especially true of patients who have learned to avoid dangerous exposures. Cases presenting asthmatic symptoms show the least tendency to spontaneous improvement. On the other hand, hay fever and pollen asthma do not, as a rule, tend to shorten life. Patients presenting even very severe symptoms often live to a ripe old age. There have been a very few reports of cases in which asthmatic attacks of long duration caused death.

Hay fever most commonly has its onset between the ages of 16 and 35 years. However, the disease can appear in infants. The youngest case on record appears to be that of Wittgenstein's¹⁹¹⁶ own child, who presented characteristic symptoms at the age of 8 months. But, as Wittgenstein took care to point out, it was possible to make this diagnosis only because both he himself and his older son also suffered from the disease. He was therefore especially inclined to think of the possibility of hay fever when he observed the infant's "cold" appearing during the hay fever season and not clearing up until the season was over. Aside from this case, reports on age incidence at the time of the first appearance of pollinosis—and especially those relating to the first year of life—differ extraordinarily, depending on whether they are based on the material of an allergist (e.g., Scheppegehl¹⁹²⁷) or of a pediatrician (e.g., Bray¹⁹). Table 42 summarizes these data.

According to Stoesser,¹⁹¹ only a few children manifest signs of hay fever during their first year of life, many more in their second year, and then there is a rapid increase in incidence in the preschool age. The present writers have seen more and more children with hay fever every year, and also, regrettably, children with pollen asthma, so that they are of the opinion that allergization of the youth living in large cities is definitely increasing. All age groups between 5 and 14 years are afflicted, and most particularly children between the ages of 7 and 12 years.

On the other hand, hay fever can also make its first appearance in persons of advanced age. Thus, Clarke and Leopold⁶⁷ reported the case of a retired admiral who had spent most

the same time of the year; (2) the symptoms are always of the same type, though over a period of years they may undergo some change, in that the conjunctival and nasal symptoms retrogress and are dominated by asthmatic manifestations, (3) there is marked improvement or even disappearance of the disease symptoms following a stay in a closed or air-conditioned room or the onset of rain, (4) although subject to certain individual and sometimes unexplainable variations, the symptoms will correspond roughly with the airborne pollen counts of the causative pollen or pollens, provided the observations are made more or less in the patient's vicinity, and more especially with regard to whether the count at any given time exceeds or falls below the patient's "critical" level of tolerance.

When these four points are duly borne in mind, the physician will not make the mistake of confusing pollinosis with allergic rhinopathy—aside from those exceptional instances that will be discussed below. The writers, therefore, reject the terms "seasonal hay fever" and "perennial hay fever," since they both make use of the designation hay fever and thus lead to confusion and error. It is important to remember, above all, that allergic rhinopathy—the writers' name for a vasomotor rhinitis of allergic origin—is in no way dependent upon the pollination seasons of trees, grasses, or weeds. And even if the condition should assume a periodic character as the result of coincidental regular exposure to allergens other than pollens at certain seasons, and thus simulate hay fever symptoms, the differential diagnosis can be made with relative ease by appropriate interrogation, testing, and on the basis of the observation that the attacks are of relatively brief duration.

A case reported by Molinié will serve as a good illustration: a hairdresser, who regularly applied iris powder (orris root) to ladies' hair at carnival time, invariably suffered sneezing spells, lacrimation, and nasal discharge at this time. Another case is that of a druggist who annually received and prepared large shipments of roses in the month of June and always became afflicted at this time with a severe "cold" and sneezing spells, which persisted as long as the roses remained fresh. (It should be borne in mind that cultivated roses do not

TABLE 42—Ages of Onset of Hay Fever According to Scheppegrell¹⁸⁸ and Bray⁹

Age Period (Years)	Percentage (Scheppegrell)	Percentage (Bray)
1-9	2	59
10-19	12	21
20-29	21	12
30-39	33	6
40-49	17	
50-59	12	2
60-70	3	

of his life either at sea or in countries where there was no ragweed, and who exhibited his first hay fever symptoms at the age of 76 years.

Sex does not appear to be of any significance in this respect.

7. DIAGNOSIS

One might expect that it would be easy enough to recognize a typical form of hay fever, with its manifestations of irritation of the nose and eyes. And yet it is a common occurrence for the patient—and the physician as well—to think at first only of an infectious "cold," especially when the patient is a child in whose immediate family there is no history of hay fever.

The four following clinical features are characteristic of the disease: (1) unless adequately treated, persons who have once acquired hay fever regularly suffer annual recurrences at

¹⁹¹ STOESEER, A. V. Journal Lancet 62: 174, 1912

shed pollen) In this connection there may be mentioned also those attacks of rhinopathy that appear after ingestion of certain kinds of fruit. However, even when these attacks of nasal or asthmatic symptoms appear in the spring or early summer, the differential diagnosis may easily be made by taking a careful history and by considering the four characteristics outlined above.

On the other hand, there are also some well founded exceptions to the rule that hay fever is dependent upon a given pollination season. For example, any patient who is regularly afflicted with hay fever symptoms in the summer or fall, may also present these manifestations in the winter if he is exposed to contact with flowers sent from the south, for example. The same may happen if he uses insecticides containing pyrethrum, for many fall hay fever cases are hypersensitive to the pollen of pyrethrum (Feinberg¹⁹³²). Furthermore, patients will suffer at any month of the year in different latitudes, provided the local vegetation to which they are sensitive is in bloom. Thus in Bombay grass pollination takes place in the months of November and December, in Cairo, in February, and so on. Lastly, pollinosis, properly speaking, must not be confused with certain conditions of nasal irritation that are likewise elicited by plant products early in the summer. We refer to the mechanical irritation of the mucous membranes by the so called "hairs" of royal palms, plane trees, etc.

ETIOLOGIC DIAGNOSES

For quick identification of the pollen responsible in a given case of hay fever, it is necessary, above all, to take a thorough history with regard to the time and place of the onset of the attacks, as well as to the nature of the local flora. The pollination calendars found below will be particularly helpful, since they present a summary of the pollination times of the most important plants to be considered in this connection. When the nasal and skin tests are negative, it is advisable to expose slides, coated with an adherent solution* outside of the windows of the patient's

room. The pollens caught on these slides are identified by a botanist. If there are any that have not been tried on the patient's skin or nasal tests are performed to ascertain whether or not they are allergenic for the particular patient. In this manner the authors succeeded in a few cases, in determining that the pollens of certain trees, bushes, and flowers that very rarely act as allergens were actually the causal agents.

(1) Pollination Calendars

A prerequisite for successful diagnosis and treatment of pollinosis is an accurate knowledge of the plants and pollination times in the patient's locality. In order to become acquainted with the local flora, the physician should undertake pollen counts himself. This is done by covering a microscope slide with a thin layer of white vaseline, glycerin or cedar oil, and exposing it for twenty-four hours in some suitable spot (window sill, roof ledge, etc.), the slide should be placed in a horizontal position, and must be reasonably sheltered from sun and possible rain. After exposure, the pollens on the slide are compared with specimens in a reference collection which can either be purchased or made with known pollens. The pollen grains are counted under low magnification, according to Durham, it is convenient to make the count for 18 sq. cm. of the slide. During the summer and fall many metropolitan newspapers publish daily "pollen counts" made by various observers but in the opinion of M. Walzer and the authors these are not too reliable since they are generally made only in one place (usually the center of the city) instead of at five or ten widely separated points and they certainly do not accurately reflect the conditions of exposure of persons living in suburban areas.

Alternate methods chiefly of investigative value involve removal of pollen grains and similar small floating particles from the air by means of impingement with centrifuge or vacuum apparatuses by electrostatic precipitation or by filtration.

Because of its simplicity, the gravity method of air sampling is the one most commonly employed, despite its recognized shortcomings. The numerical values of the counts by the gravity slide method are only very rough and inaccurate indications of the actual volumetric

¹⁹³² FEINBERG S M J A M A 102 1557 1934

* For this purpose a fine film of petrolatum, glycerin or cedar oil or glycerin jelly with or without the addition of methyl green may be used.

values of the pollen grains per cubic yard of air as determined by volumetric devices (Durham¹⁹³³). This is due to variations in the size, specific gravity, and surface characteristics of the grains, and in wind velocity. However, for practical purposes such numerical data are not of greater clinical significance than the simple observation of the appearance in the air of a given species of pollen in numbers sufficient to produce clinical symptoms, and the determination of the period during which clinically significant numbers are present (Gottlieb and Urbach¹⁹³⁴).

Since the physician does not always have the time or facilities for performing such counts himself, pollen surveys that have been made in many locations in the United States will be found helpful. Naturally no single pollen calendar can apply throughout an area as vast as America. Thus, according to A. D. Hopkins,¹⁹³⁵ other conditions being equal, the variation of the pollination time in temperate North America occurs later to the northward and eastward in the spring and early summer, the reverse being true in late summer and autumn. This progression takes place at a general average rate of 4 days to each degree of latitude and every 5 degrees of longitude. The average advance of the season per day is 17 miles northward and 62 miles eastward. Even in areas at the same elevation, there are often variations of weeks between the beginning of the antherperiod in one district as against another, depending on the geographic location. The topography of the land, and particularly the altitude, the climate, the character of the soil, conditions resulting from cultivation, rainfall, and sunshine, all are factors making for considerable differences. The ideal, of course, would be a pollen calendar for every large city and for every 100 square miles or so of territory.

Since no such collection of data exists, Gottlieb and Urbach¹⁹³⁶ have endeavored to gather all the available material and to compile from it nine graphs, each one representing an area in

which like phenologic conditions prevail.* This is intended to serve as a sort of guide to the various types of pollens with which the physician may have to test his patient, as well as to the dates on which the manifestations of hay fever may be expected.

Naturally, certain sources of error are inherent in pollen surveys, whether made by atmospheric count or by botanic observation. In the first place, the beginning as well as the end of the pollination period depends from year to year on meteorologic factors, particularly the range of temperature, the percentage

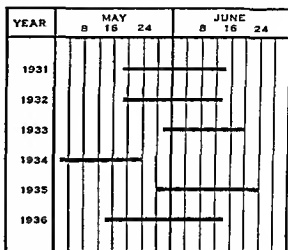


FIG. 250 POLLINATION TIMES OF ONE PLANT (ORCHARD GRASS, *Dactylis glomerata*) IN SIX SUCCESSIVE YEARS IN ONE LOCATION

Note marked variation (as much as four weeks) in onset and cessation of pollination in certain years

of sunshine, and the amount of precipitation. Thus, an especially warm spring and summer, with heavy rainfall, will appreciably advance the date of the first blooming, whereas a cold and dry pre-season will delay it. The pollen calendar cannot do more than give the average dates. FIGURE 250 shows how, under certain circumstances, flowering can be hastened or retarded by as much as from two to four weeks. It will be seen that the onset of pollination of orchard grass (*Dactylis glomerata*) was found in one locality to vary in six consecutive years from May 2 to May 29.

In the second place, extraordinary weather conditions can quite suddenly convert to major

* D. D. DURHAM, O. C. J. Allergy 15: 226, 1944

** GOTTIEB, P. M., and URBACH, E. J. Lab. & Clin. Med. 28: 1426, 1943.

*** HOPKINS, A. D. cited by Ellis, R. V., and Rosendahl, C. O. Minnesota Med. 16: 319, 1933

**** GOTTIEB, P. M., and URBACH, E. J. Lab. & Clin. Med. 28: 1033, 1943

* The term "plant phenology" designates the dependence of the seasonal manifestations of plant life on climatic and geographic conditions.

factors pollens that under normal circumstances are relatively unimportant in a given area. Thus, Feinberg and Durham¹⁹⁹⁷ reported that in the Chicago area in 1934—in contrast with other years—the pollens from certain trees and from certain *Chenopodiales* (e.g., Russian thistle) were the principal allergizing agents. Duke¹⁹⁹⁸ made the opposite observation, namely, that pollens ordinarily abundant in Kansas City, Mo., were either absent or nearly so in a season with unusual weather conditions.

Furthermore, in isolated cases—owing primarily to uncommon conditions of exposure—individuals may be allergized by the pollens of trees, flowers and bushes that only very rarely cause hay fever. For example, Dutton¹⁹⁹⁹ and Phillips²⁰⁰⁰ showed that in fields near El Paso, Tex., and Phoenix, Ariz., respectively, where the common sugar beet (*Beta vulgaris*), a member of the family *Chenopodiaceae*, is intensively cultivated, some cases of hay fever are due to its pollen, which is shed from early May to mid June. Plans to augment greatly the acreage devoted to this plant may well lead to an increase in the number of such cases. McMinn and Graham²⁰⁰¹ found that the pollen of the mirror plant (*Coprosma baueri*), an ornamental shrub widely planted in California and pollinating from the beginning of April to the end of June, yields positive skin tests in a considerable group of patients with hay fever. Langley²⁰⁰² reported an unusual case of hypersensitivity in a nurseryman to the pollen of an exotic plant *Piqueria trinervia*, as a result of hothouse exposure during the winter. The senior writer encountered 2 exceptional cases in which hay fever was evoked by the pollens of tree of heaven (*Ailanthus glandulosus*) and horse chestnut (*Aesculus hippocastanum*) respectively. Mention should also be made here of the possibility of allergy to insect borne pollens under appropriate conditions.

A third important source of error lies in the fact that even within a relatively small area differences in elevation above sea level play a

significant part in advancing or delaying the date of first pollination by as much as a month or more. This applies, for example to the differences in the anther periods as between a valley and adjacent mountains. Thus Hopkins¹⁹⁹⁵ determined that for each 100 feet of altitude the delay amounts to about one day. It is also well known that the nature of the flora present varies greatly with increasing altitude.

Despite all these obvious and inevitable faults, such tabulations of data as the pollen calendars are certainly of great general value to the physician and have indeed proved themselves to be very helpful in practice.

The tree, grass, and weed seasons may, to a certain extent, overlap. Thus, the season of tree pollination sometimes extends into that of grass pollination. There are, of course, considerable areas in the south where the flora is in bloom through the entire year. All this is clearly indicated in the accompanying tables.

In the last twenty eight years, 173 papers have been written on the subject of the distribution and pollination times of plants producing hay fever in smaller or larger areas of the country. The cities and regions from which these surveys have been reported are graphically shown in FIGURE 251. From this it may be seen that certain rather extensive areas have never been covered. In a critical review of existing pollen surveys, this and other deficiencies were fully discussed by Gottlieb and Urbach.¹⁹⁹⁴

It has hitherto been customary in such work to divide the United States into districts according to state boundaries or into the usual geographico-economic units. From the phenologic point of view however this approach is obviously incorrect. Even where states are bounded by rivers, the same flora is practically always established on both banks. Hence, we have more logically resorted to the botanic vegetational areas painstakingly delineated by Livingston and Shreve.²⁰⁰³ It was found necessary to modify the map of these authors to accord with the fact that we are solely concerned with plants capable of producing hay

¹⁹⁹⁷ FEINBERG S. M. and DURHAM O. C. Ann. Int. Med. 8: 1282 1935.

¹⁹⁹⁸ DUKE W. W. J. Allergy 2: 471 1935.

¹⁹⁹⁹ DUTTON L. O. ibid. 9: 607 1938.

²⁰⁰⁰ PHILLIPS E. W. ibid. 11: 28 1939.

²⁰⁰¹ McMINN H. E. and GRAHAM E. ibid. 8: 194 1937.

²⁰⁰² LANGLEY W. D. ibid. 9: 60 1937.

²⁰⁰³ LIVINGSTON B. E. and SHREVE F. The Desert and on of V egetation on the United States as Related to Climatic Conditions. Pub. 284. Carnegie Institution of Washington 1921.

fever, rather than with all the flora. FIGURE 252 presents a division of the United States, according to these principles, into nine zones

By combining and, so to speak, "averaging" for each zone the score or more surveys made in separate localities, comprehensive data were obtained. The results are given in FIGURES

bination of observations from widely separated localities, climatic variations, differences in the time of planting of cultivated species, and other factors. This is especially true in regard to the spring and early summer seasons, more so than with respect to the late summer and fall

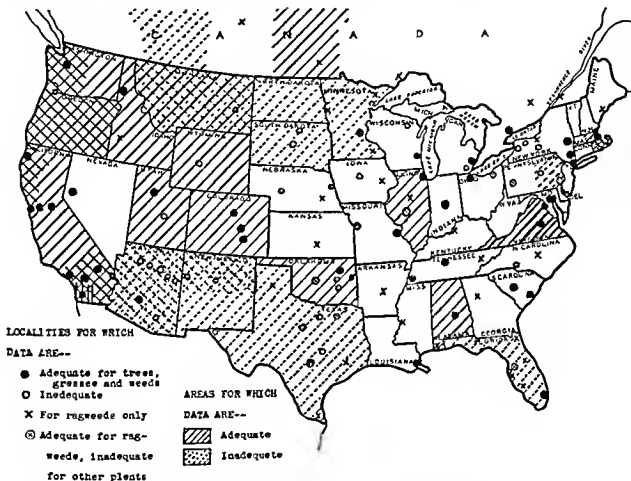


FIG. 251. SPOT MAP OF LOCALITIES AND AREAS OF UNITED STATES FOR WHICH POLLEN STUDIES HAVE BEEN REPORTED

Second survey in same region is indicated by cross-hatching

253 to 261, which constitute pollination calendars for each of the nine zones.

Not all the plants mentioned in the literature are included in the graphs. Only those of considerable importance were selected. The main pollination times are represented in heavy unbroken bars. This tends, in most instances, to show somewhat greater length than is true of the actual season at any one place in any one year, because of the totaling of the commoner annual deviations, the com-

It should also be pointed out that many plants pollinate sporadically both before and after the principal season, that local circumstances may influence the dates over a limited area, and that unusual weather conditions may correspondingly accelerate or delay pollination. All this is signified in the calendars by the interrupted lines. Finally, the various trees, grasses, and weeds have been graded, according to their frequency and importance, into three groups: those that play a major part

in the causation of hay fever, those of secondary significance, and those of lesser consequence. This is indicated in the designations on the graphs by boldface, capitals and ordinary type respectively.

Needless to say, other plants besides those listed in these calendars may less often be responsible for occasional cases of pollinosis whether as a result of unusual exposure or of extraordinary weather conditions. For localities near the boundary of a zone, it is suggested

proximately coincides with the southern coastal plain, with a northward extension along the Mississippi delta to the southwestern tip of Kentucky. Roughly this includes the southern part of South Carolina, the southern two thirds of Georgia and Alabama, northern Florida, the western tip of Tennessee, Mississippi, Louisiana, and southeastern Texas. The season extends from May to September or October and tends to be longer in the more southern reaches of the region. The incidence

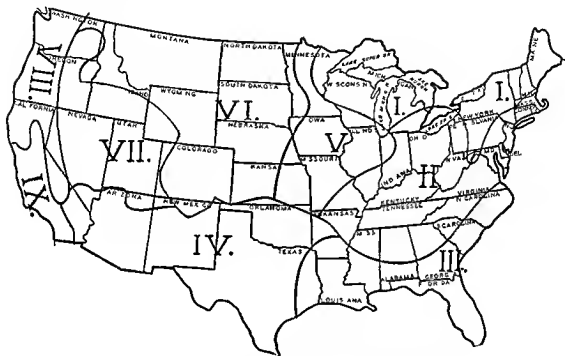


FIG. 252 SCHEMATIC DIVISION OF UNITED STATES INTO NINE POLLINATION ZONES WITH RESPECT TO HAY FEVER PRODUCING PLANTS

that the calendar for the adjacent zone also be consulted.

It should also be noted that there is a form of summer hay fever of unknown origin, also referred to as 'X hay fever,' in the southeastern states, and accounting for more than half of the cases during that season, or approximately 10 per cent of all hay fever in the region. The symptomatology is typical, often complicated by asthma, and eosinophils are present in the nasal secretions. According to replies to a questionnaire by Wodehouse⁵⁵⁹ and Efron, the distribution of this condition ap

pears to be greater in the more southern section, particularly in New Orleans. Symptoms are worse at night and in the early morning. Although the season corresponds fairly closely to the period of grass pollination, all skin and conjunctival tests with pollens are negative. On the basis of a correlation in distribution, Weil²⁰⁰⁴ suggested the possibility that sensitivity to the citrus white fly or to the pecan scab (*Cladosporium effusum*), a fungus, might be responsible, but

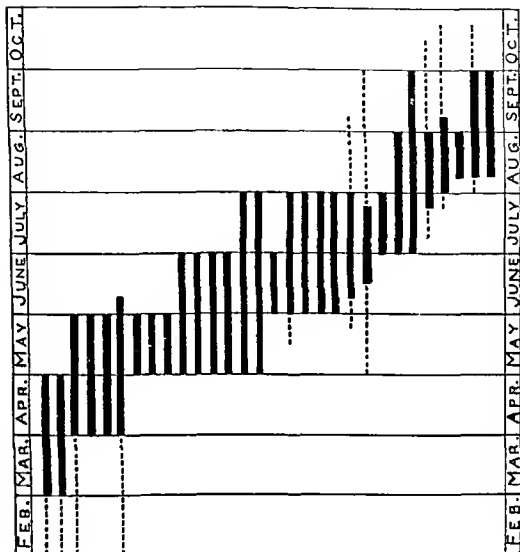
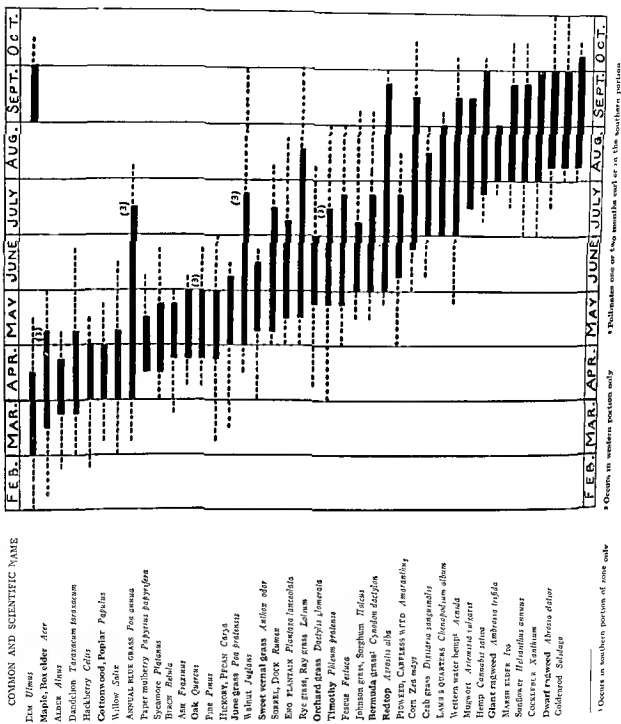


FIG. 253 POLLINATION CALENDAR FOR ZONE I

* Occurs in western portion of zone only



COMMON AND SCIENTIFIC NAME.

[illegible]

Occurs in Florida only

Occurs in southern Florida only

Name in French

at Napa in county no. 11, 1860.

ERIC 255 POLLINATION CALIPAR FOR ZONT III

COMMON AND SCIENTIFIC NAME

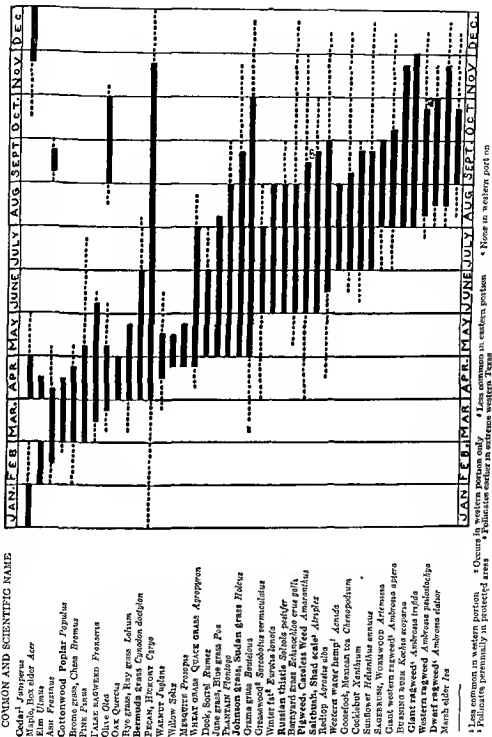


FIG 256 POLLINATION CALENDAR FOR ZONE IV

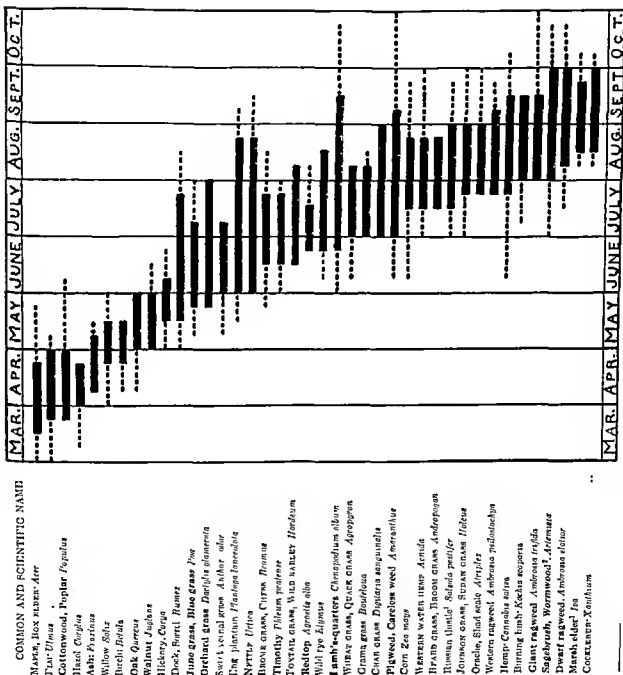


Fig. 257. POLLINATION CALENDAR FOR ZONE V
 * None in Milwaukee, Wis. * Very little in Omaha, Neb., and Milwaukee, Wis.

COMMON AND SCIENTIFIC NAME

	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT
Elm <i>Ulm</i>								
Alder <i>Alnus</i>								
B h <i>Betula</i>								
V low <i>Salix</i>								
Cottonwood Poplar <i>Populus</i>								
Box elder Maple <i>Acer</i>								
J n per <i>Juniperus</i>								
Oak <i>Quercus</i>								
DANDELION <i>Taraxacum officinale</i>								
W nt n <i>Valeriana officinalis</i>								
Ash <i>Fraxinus</i>								
Orchard grass <i>Dactylis glomerata</i>								
June grass Blue grass <i>Poa</i>								
FORTALL GRASS <i>Valeriana</i>								
P ns <i>Poa</i>								
Fescue <i>Festuca</i>								
Wheat grass Quack grass <i>Alopecurus</i>								
SOARUM, DOCK <i>Rumex</i>								
Johnson grass Sudan grass <i>Heteropogon</i>								
BROME GRASS <i>Cynodon</i>								
SALT GRASS <i>Dactylis</i>								
W ld yr <i>Lycium</i>								
SAL <i>Salix</i>								
Lamb's quarters <i>Chenopodium album</i>								
Timothy <i>Phleum pratense</i>								
Rudbeckia <i>Aster</i>								
PLANT <i>Plantago</i>								
Russian thistle <i>Sesuvium</i>								
Ploweed Tumbleweed <i>Amaranthus</i>								
Co n <i>Cornus</i>								
Marsh elder <i>Ilex</i>								
Co RLES n <i>Xanthoxylum</i>								
W ESTERN WATER HEMP <i>Aster</i>								
Burning bush <i>Koeleria</i>								
Clant ragweed <i>Ambrosia</i>								
C anna g us <i>Bonifera</i>								
Western ragweed <i>Ambrosia</i>								
Sagebrush <i>Artemisia</i>								
Fals ragweed <i>Fragaria</i>								
Dwarf ragweed <i>Ambrosia</i>								

None n wets n Co n do we c n Mo ana o wo he = 10 days

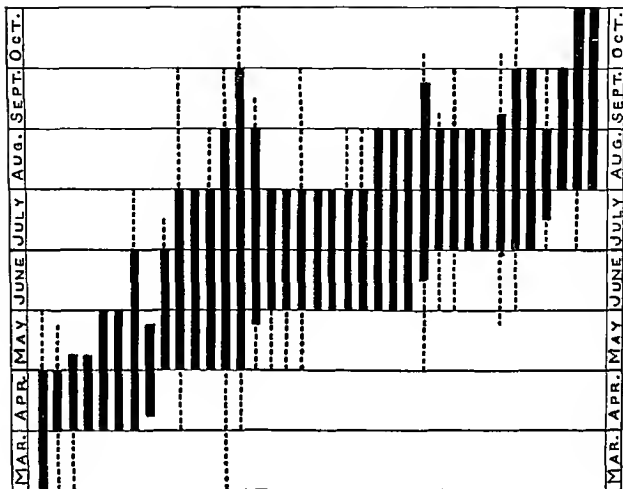
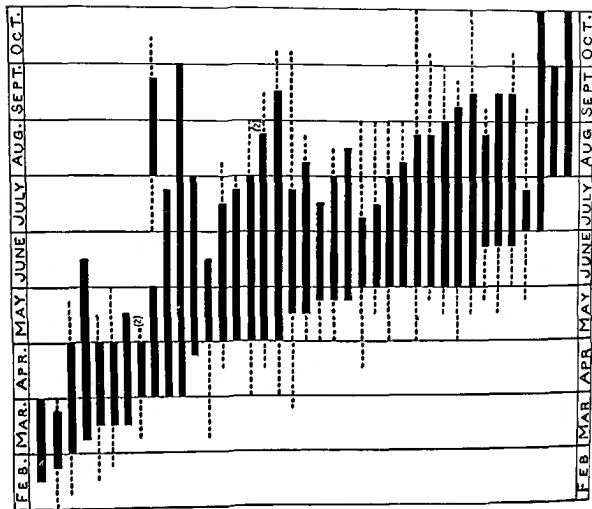


FIG. 259. POLLINATION CALENDAR FOR ZONE VII

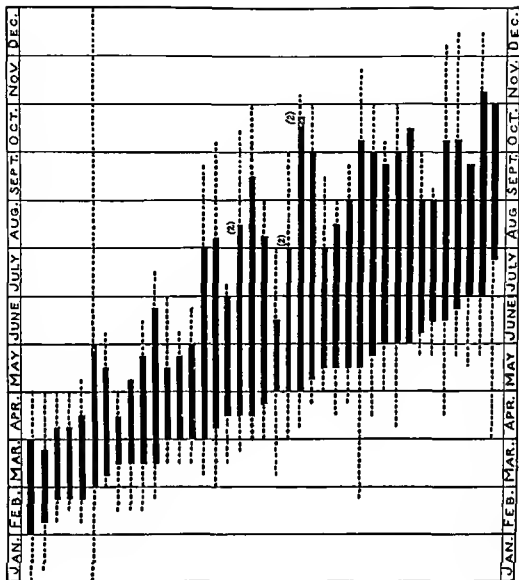


COMMON AND SCIENTIFIC NAMES

Hazel *Corylus*
 Alder *Alnus*
 Willow *Salix*
 Oat wild and cultivated *Avena*
 Box Elder *Maple* *Acer*
 Oak *Quercus*
 Acacia *Acacia*
 Cottonwood *Populus*
 Populus *Populus*
 False Ragweed *Franseria*
 Salt Grass *Dactylis spicata*
 Dandelion *Taraxacum taraxacum*
 Cockspur *Xanthoxylum*
 Sweet vernal grass *Anthriscus*
 Bromus *Bromus*
 Barley *Barley* *Hordeum*
 Johnson grass *Urtica*
 Dock *Sorrel* *Rumex*
 End plantain *Polygonum lanceolatum*
 June grass *Blue grass* *Poa*
 Rye grass *Rye grass* *Lolium*
 Fescue *Festuca*
 Orchard grass *Dactylis glomerata*
 Wild rye *Elymus*
 Canary grass *Plinia*
 Velvet grass *Velvet grass*
 Wheat grass *Quack grass* *Agropyron*
 Timothy *Poa pratensis*
 Bermuda grass *Cynodon dactylon*
 Lamb's quarters *Chenopodium album*
 Nettle *Urtica*
 Sheep scale *Aster*
 Pigweed *Tumbleweed* *Amaranthus*
 Redtop *Alopecurus*
 Purple wattle *Salicornia ambigua*
 Sagebrush *Mugwort* *Artichoke*
 Bent grass *Alopecurus*
 Russian thistle *Salicaria*
 Marsh elder *Juncus*
 Ragweed *Ambrosia trifida*

* Note: northern port on

* Pollenates: none! earlier in southern port on



1 Less common in southern portion

2 Pollinates frequently in certain areas, especially in southern portion

FIG. 261. POLLINATION CALENDAR FOR ZONE IX

this has not been corroborated. Studies by a committee²⁹⁷ and by individual investigators have yielded no evidence implicating air borne fungus spores, smuts, seventeen species of insects, commercial fertilizers and insecticides. It has even been suggested that the cause may be sensitization to a virus exposure to which is seasonal (Rockwell). Further investigations are being conducted, with particular reference to fungi.

(2) Allergy Testing

Before considering the type of testing to be employed, it is necessary to discuss the question of whether to use mixed or single extracts. The present writers agree with Scheppegegrell²⁹⁷ and others that the mixed extract will frequently lack the particular pollens that are of importance in a given case, and that it is therefore preferable to make tests with single extracts, according to the local flora.

Since the best therapeutic results are obtained when the patient is treated with all of the pollens capable of eliciting his hay fever, it is essential to identify them. For this purpose, the patient is usually subjected to scratch or intracutaneous testing. Unfortunately it must be admitted however that neither a positive nor a negative result of such tests is always diagnostically dependable. Thus Kern,²⁹⁸ Kahn,²⁹⁹ Wilmer,³⁰⁰ Peshkin,³⁰¹ Colmes,³⁰² the senior author,³⁰³ and others have observed that from 2 to 13 per cent of their pollinosis cases gave negative skin but positive ophthalmic or nasal reactions. Moreover, some patients, seen at the very beginning of their hay fever, may give negative skin tests, the reactions being positive the following year. On the other hand, the intracutaneous method very frequently elicits reactions even if there is no nasal hypersensitiveness to the pollens (Rackemann and Smith³⁰⁴ Scheppegegrell,³⁰¹ Farmer Loeb and Petow,³⁰⁵ and others). Baldwin³⁰³ reported positive skin reactions and even successful passive transfer in indi-

viduals who did not have hay fever and did not contract it later. Freeman and Hughes³⁰⁴ Grubb and Vaughan³⁰⁵ and others demonstrated that patients may give positive reactions to pollens with which for geographic reasons they could never have come into contact. Blumstein and Tuft³⁰⁶ reported that none of their patients with purely autumnal hay fever was clinically sensitive to plantain, although 18 of them gave positive skin tests. Nevertheless, skin tests have the great advantage that they may be performed—with due caution—during the hay fever season, while this is not advisable with nasal and ophthalmic tests except in an air conditioned room.

As pointed out in some detail elsewhere the scratch method, while the least sensitive, is also the most specific. One can either apply a small quantity of pure pollen on a scarified skin site moistened with N/20 sodium hydroxide solution, or a 2 per cent solution prepared by pharmaceutical firms and put up in capillary tubes. Only if this method fails to evoke a reaction should one proceed with the intracutaneous injection of 0.02 cc of a 1:10,000 pollen solution, and if this is negative, with a 1:1,000 solution. A reaction is interpreted as positive when the injection site presents a wheal (possibly with pseudopodia) exceeding 1 cm in diameter, along with surrounding erythema. It is not advisable to inject several concentrations at one time for their cumulative effect may bring on systemic reactions, nor for the same reason should too many related species of pollen be injected simultaneously.

The writers are of the opinion that the nasal test simulates the actual conditions of exposure far more closely than does any other test (Urbach³⁰⁷). However, it must be remembered that only minute quantities should be insufflated (about as much as can be placed on a small platinum loop or on the smaller end of a toothpick). A positive reaction is manifested by sneezing and watery secretion or nasal obstruction, while the control insufflation of talcum should not elicit any response. A positive result on nasal testing nearly always

²⁹⁷ KERN R A. *Ann Clin Med* 5: 371, 1926.

²⁹⁸ KAHN I S. *South M J* 21: 559, 1925.

²⁹⁹ WILMER H B. *J Allergy* 1: 87, 1929.

³⁰⁰ PESHKIN M M. *ibid* 3: 20, 1931.

³⁰¹ COLMES A. *New England J Med* 225: 817, 1941.

³⁰² RACKEMANN F M and SMITH L B. *J Allergy* 2: 364, 1931.

³⁰³ SCHEPPEGRELL W. *New Orleans M & S J* 78: 132, 1925.

³⁰⁴ LOEB L F and PETOW H. *Kl a Wechschr* 9: 987, 1930.

³⁰⁵ BALDWIN L B. *J Immunol* 13: 345, 1927.

³⁰⁶ FREEMAN J and HUGHES W H. *Lancet* i: 941, 1938.

³⁰⁷ GRUBB G D and VAUGHAN W T. *J Allergy* 9: 211, 1938.

³⁰⁸ BLUMSTEIN G I and TUFT L. *J A M A* 108: 1, 1937.

³⁰⁹ URBACH E. *Muenchen med Wchschr* 80: 134, 1933.

indicates the presence of hypersensitiveness to the pollen used. The disadvantages inherent in this method are, as Blumstein²⁰¹⁸ points out, that the patient may suffer from hay fever symptoms for several hours, and furthermore that when a test is positive, no more tests can be performed at the same sitting. However, when symptoms make their appearance, they can be rapidly controlled by the use of vasoconstrictors, such as 1 per cent neosynephrin or 3 per cent propadrine solution. For these reasons, this method is more time-consuming and requires more visits, however, in the writers' opinion, these disadvantages are more than outweighed by its greater specificity. It is important to note that in cases of isolated pollen asthma, the nasal method fails to evoke reactions; in these instances, specific reactions can be obtained by having the patient inhale highly diluted pollen solutions (see p. 185).

The ophthalmic test is performed with minute quantities of either dry pollen or liquid pollen extract applied to the conjunctiva of the lower eyelid. As a control, talcum powder is similarly applied to the other eye. A positive reaction is manifested within a few minutes by itching, marked redness, and sometimes swelling of the mucosa, while the control eye remains unchanged, subjectively and objectively. The local symptoms can be managed promptly by administration of the eye drops mentioned on page 559. Peshkin²⁰⁰⁸ and others have observed positive ophthalmic tests in patients giving negative skin tests. Tuft,¹² however, mentions the occurrence of positive eye and skin reactions both without clinical evidence of hay fever.

Tests for hypersensitiveness to scents are performed by exposing the patient to the odoriferous blossoms suspected, at a time when he is free of symptoms.

In every case of hay fever, intracutaneous tests with dust, and sometimes with autogenous dust, should be performed. For, in the experience of the present writers and of others, failure to recognize the presence of a concomitant allergy to dust may well be the principal reason for the failure of hay fever therapy in certain cases. Furthermore, whenever the history suggests the existence of food allergy, or of allergy to an inhalant other than

pollen, appropriate skin tests or preferably exposure trials should be made. The same applies to those cases in which specific treatment produces unsatisfactory results.

Serologic Tests.—It would, of course, be far simpler and far less hazardous if one could perform *in vitro* such tests as precipitation, agglutination, cytotoxicity, and particularly complement fixation tests. These tests would make it possible to arrive at a diagnosis without requiring the patient to be present; a few cubic centimeters of blood taken from the patient while he is in the country, for example, could be sent to the laboratory of a diagnostic institute in the city, and would suffice for the purpose of performing serologic reactions. Unfortunately, however, despite numerous efforts in this direction, no practical results have as yet been achieved (Cohen and Weller,²⁷⁹ Hensel and Sheldon¹⁹⁰⁷). It is true that Neisser, Sachs, Klopstock, and Witebsky have shown that the complement fixation method is useful for demonstrating an antigen-antibody reaction; in practice, however, it has been found that too many sources of error still obtain in this method.

Albus²⁰¹⁹ alone claimed to have succeeded, in a high percentage of cases, in serologic identification of the allergen in pollen hypersensitiveness. The technic he employed corresponded to the Hecht modification of the Wassermann test. The results of investigations by the senior author, in association with Brandt, regrettably do not permit a full confirmation of the optimistic claims of Albus. But it can by no means be denied that in principle it should be possible, in these conditions, to identify the allergen by serologic methods.

8. THERAPY

There can be no doubt that the intensity and the course of hay fever can be appreciably diminished and abbreviated when appropriate prophylactic measures can be applied. The prophylaxis may be divided into the nonspecific and the specific measures.

a) NONSPECIFIC PROPHYLAXIS

This approach is of relatively little value, since not many patients have the time and the

²⁰¹⁸ BLUMSTEIN, G. I. *J. Allergy* 8, 321, 1937.

²⁰¹⁹ ALBUS, G., *Ztschr. f. d. ges. exper. Med.* 96: 710, 1935.

funds to employ this method. It consists in sending the patient to localities either where the plant to whose pollen the patient is sensitive does not grow, or where the given plants have not yet or have already pollinated. In cases of hay fever due to grasses, an ocean voyage or sojourn in the mountains or in the desert is the only solution to the problem. Patients who are allergic to ragweed pollen may go to the White Mountains, the northern part of Michigan, west of the Rocky Mountains, or most heavily forested regions. It must always be remembered, however, that this change of climate is of limited value, since it does not help to increase the patient's tolerance.

Although the total destruction of "stands" of ragweed has been sporadically attempted at various localities from time to time, little if anything has been accomplished thereby, and it is obvious that such an effort on a sufficiently wide scale is a task of well nigh inconceivable magnitude. However, there have recently been developed chemical sprays (the most promising of which to date is apparently "2-4-D") capable of preventing flower formation or at least pollen production and of efficient widespread dissemination (Gringsby²⁰²⁰). While details of method remain to be worked out, it is quite within the realm of possibility, with the information already available, to develop a broad program designed to eliminate the production of pollen by the common ragweeds, without the undesirable features of the destruction of other vegetation including cultivated crops, or of possible danger to livestock. Such a project would prove of immense benefit to the multitudes of hay fever sufferers.

Hay fever patients should sleep with their bedroom windows closed, although they may possibly be left open between the hours of 10 P. M. to 4 A. M., after which time many grasses and weeds begin to shed their pollens. Air conditioning the bedroom, if feasible, will accomplish the same purpose more efficiently and comfortably. In the daytime, it is best to keep the windows closed, and to exclude plants and fresh cut flowers from the home. Laundry that is put out to dry on the lawn should be carefully shaken out before ironing. On coming home, patients should take off their outer garments before entering their

bedrooms. The patient's garments should not be shaken out or brushed out of doors in the summer. Flat surfaces including floors and window sills should be wiped daily with a moist or oiled cloth. Since hair will carry quantities of pollen, animals should not be allowed in the bedroom. Patients undergoing specific treatment should also avoid massive exposure (trips by railroad or automobile, long walks or work in the open) since the state of insensitiveness achieved by treatment is not, as a rule, absolute. If possible it is best to stay indoors on windy days. The common commercial insecticides which contain pyrethrum should be avoided. When cosmetics, the contents of bedding, or mildew and molds in bedding are suspected of being associated allergens, hypoallergenic cosmetics or allergen-proof mattress and pillow encasing should be employed. It is advisable to recommend adequate rest and the avoidance of emotional upsets, noxious fumes, irritant dusts, and possibly even excessive smoking.

b) SPECIFIC PROPHYLAXIS

With the exception of the coseasonal method, the techniques to be described below also belong to the prophylactic measures, since institution of these—some months before the beginning of the hay fever season—is intended to prevent the appearance of hay fever manifestations. They include hyposensitization and deallergization methods, which will be discussed in separate sections.

A distinction is made, in principle, between two routes of administration: the parenteral and the enteral. The parenteral approach comprises the subcutaneous and the intracutaneous methods. (The use of nasal sprays of pollen extracts will not be discussed because it has not as yet proved to be satisfactory.)

But it is not so much the route as the mode of administration that determines whether the particular method is properly regarded as a hyposensitization or a deallergization procedure. As outlined on page 201, the principal difference between the methods of hyposensitization and of deallergization is that in the former one attempts by injections of graduated doses of antigen to increase the quantity of antibodies circulating in the blood, while in the latter the object is to neutralize

the available tissue antibodies by producing a so-called microshock, thereby eventually inhibiting the production of specific antibodies. The difference between these two most important therapies in hay fever is, therefore, rather a qualitative than a quantitative one.

It is generally believed that the preseasonal, perennial, and coseasonal methods actually increase the antibodies in the blood, consequently preventing the pollen allergen from coming into contact with the sessile antibodies in the mucous membranes, and thus from entering into an antigen-antibody reaction. These methods, while often beneficial, are of limited value because the titer of the circulating antibodies declines a few weeks after treatment is stopped, without a similar decrease of the cellular antibodies. However, when the treatment is continued perennially for many years, the antibody titer in the blood and tissues may gradually decrease, according to the investigations of Sherman and Stull,³⁵⁹ thus leading to a state of deallergization. Freeman's rush method,³⁶⁴ on the other hand, achieves at least a temporary deallergization, i.e., a temporary saturation of the cellular antibodies. In the writers' opinion, oral administration of pollen is to be regarded as a skephotylactic method of treatment, and therefore leads, when appropriately administered, to what is at first a temporary deallergization, which after a few years becomes permanent. For a detailed discussion of the theories on which these methods are based, the reader is referred to the sections on deallergization (p. 212) and hyposensitization (p. 202).

In a series of studies designed to place hay fever therapy on a sound immunologic basis, Loveless³⁶⁵ demonstrated that a rough parallel existed between the amount of thermostable ("blocking") antibody present in the blood of preseasonally treated ragweed-sensitive patients and the degree of clinical insusceptibility they exhibited. The degree of clinical resistance associated with a given amount of thermostable antibody varied decidedly with the individual, some requiring much more antibody than others for effective immunity. The conjunctival reaction obtained with minimal amounts of antigen to determine the threshold of sensitiveness may serve as a

simple index to the patient's level of resistance. Loveless suggests that the incidence of satisfactory clinical results might be increased by treating patients according to their particular immunologic needs, rather than empirically as at present. Unfortunately, Gelfand and Frank³⁶⁵ and others have failed to confirm the finding that the clinical results of hay fever therapy parallel the titer of the blocking antibody, and the subject requires further investigation. But if a correlation can be shown, the method devised by Hampton, Johnson, Alexander, and Wilson³⁶⁶ for the detection of the thermostable antibody by means of a precipitin reaction will do much to render this approach more practical. Their technic requires only the patient's serum, ragweed extract, and a potent rabbit anti-ragweed serum. It is much simpler than the passive transfer test, and does not require a human recipient.

On the basis of the transferable protective effects of the thermostable or blocking antibody, a type of passive hyposensitization was employed therapeutically by Cooke et al.³⁶⁷ Blood transfusions from treated to untreated hay fever patients gave results which were sometimes striking. Obviously this method is not clinically practical.

Before entering upon discussion of the various methods in greater detail, it is necessary to give consideration to the choice, preparation, and standardization of pollen extracts.

There are many divergent opinions as to the kind of pollen extracts to be employed. Some authors recommend treatment with only one—the most important or "representative"—species of pollen, e.g., timothy pollen extract in the case of hay fever due to grass pollens, and a mixture of short and giant ragweed pollens in cases of hypersensitiveness to weeds. These authors assume that the plants belonging to the same botanic group are antigenically related—i.e., that they have a common antigen. Other authorities recommend the use of commercial polyvalent pollen extracts, prepared for use in the area in which the patient lives. A third school of thought favors hypsensitization procedures with an extract containing all the pollens evoking positive cutaneous or other reactions—an individualized therapy.

A number of investigators including the present writers have opposed the first mentioned method—namely treatment with an extract of the one leading pollen allergen—for patients with multiple sensitivities. Grub and Vaughan^{6,7} found when they tested 214 grass allergics with ten different grass pollens intracutaneously that 17 per cent of the patients reacted to only one species of pollen (not all of course to the same type) and 83 per cent to two or more grass pollens. The single species with the highest incidence of positive reactions was redtop to which 60.6 per cent of the group reacted. If, for example, only redtop had been used for testing, one third of the grass allergic patients would not have been detected. Furthermore, since about one sixth were found to be strictly species specific in their reactivity, they would have received no benefit from treatment with redtop extract alone.

The second method is recommended when testing cannot be performed for extraneous reasons. The objection that employment of it involves the risk of sensitizing the patient to additional previously innocuous species of pollen is likely to be of a strictly theoretic nature in the writers' opinion. The suggestion sometimes made that this method does away with the necessity for all testing is decidedly not in the interest of rational therapeutics.

Most authors now believe that the most efficacious treatment is administration of mixed pollen extracts containing all those species to which the patient gives definitely positive skin reactions. It must be borne in mind of course that hay fever patients not uncommonly react strongly to skin tests with species of pollen that do not evoke clinical manifestations. On the other hand, there are also some patients who fail to react to skin tests although they will react to nasal or bronchial tests with the same pollen. In other words, the results of skin tests are by no means a dependable criterion in every case. This difficulty can be circumvented in the writers' opinion by first performing nasal or if indicated bronchial tests and by preparing the extracts in accordance with the results of such tests.

The preparation of pollen extracts is of interest to the physician only in so far as the

extracting agents are concerned. Very few doctors will trouble to prepare their own extracts since they are so readily obtainable commercially. It suffices therefore to say that dry pollens are treated with ether or carbon tetrachloride in order to remove their oily portions which on injection would irritate the skin and which would also cloud the extracts. Various extracting agents are then used to remove from the dry pollen the water or saline soluble principles responsible for hay fever. The solution employed determines the keeping properties of the pollen extracts. Those made with the phenolized alkaline saline fluid of Coca are said to deteriorate after about three months. Extracts made in solutions containing glycerin (46 per cent) as advocated by Clock appear to possess the greatest stability; they are however quite often irritating and painful.* Black suggested the addition of 1 per cent butyn to alleviate the pain. Moore and Unger advocated an extracting fluid containing 5 per cent dextrose and 0.5 per cent phenol with the addition of a sodium bicarbonate buffer. G. T. Brown insists however that this solution is less stable and subject to contamination by fungi. The consensus today is that not too strongly glycerinated extracting fluids are the best.

Efforts have also been made to prepare extracts that would be more slowly absorbed. Without going into details, the following methods should be mentioned: glycerolated extracts (Clock), alum precipitated extracts (Sledge), formalized extracts (Cooke, Stull, Hebal, and Loveless), extracts in lanolin and olive oil (Waterman), in almond oil (Feinberg and Bernstein), lyophilized pollen extract homogenized electrically into sesame oil (Taub and Rubens), extracts in gelatin (Spain, Fuchs, and Strauss), pollen tannate (Waterman), and pollen antigen hydrochloride (Rockwell). It is claimed that patients exhibit a greater tolerance to such mixtures, that a higher maximum dosage can be given with safety and with fewer injections, that constitutional reactions occur less frequently and are milder when they do occur, that more effective clinical relief can be obtained with their use, and lastly, that

* In the case of a child that had unusually severe pain one of us was able to procure a hypersensitivity to glycerin by the fact that a glycerin suppository I knew he bought once before had pain.

patients so sensitive that they accept poorly the usual aqueous pollen therapy, can better tolerate these mixtures. However, the very fact that so many different preparations have been introduced clearly shows that, while the basic ideas may be good, the preparations do not entirely achieve their goal.

The question of the standardization of pollen extracts has also received considerable attention. It is generally conceded, however, that no entirely satisfactory method has as yet been devised for standardizing the extracts accurately, as far as potency is concerned. This is because we are attempting to apply a chemical measure to a biologic activity.

In 1911, Noon²⁰² adopted as one *pollen unit* the quantity of allergen contained in an extract of 0.000001 Gm of pollen. Objections were raised to this unit on the grounds that a given weight of different samples of one species of pollen does not always contain the same quantity of the hay fever excitant, and, furthermore, that there are often great discrepancies between the weights of unrelated pollens and their content of hay fever excitant.

Similar to the Noon method is the *weight by volume* system—a given weight of pollen extracted with a given volume of fluid. For example, if 1 Gm of pollen is extracted with 1,000 cc of fluid, this is a 1:1,000 solution, which means that each cubic centimeter contains 0.001 Gm. of dry pollen. Against this method the objection was raised that the entire pollen grain is weighed rather than the active substance, and, furthermore, that the assumption that it will yield extracts of equivalent activity is erroneous (Coca²⁰³).

In 1915, Cooke²⁰⁴ introduced the determination of *total nitrogen content*, by the Kjeldahl method, as an index of protein content. His unit was expressed in terms of fractions of a milligram of total nitrogen. But, since the total nitrogen represents nonprotein as well as protein nitrogen, this determination is by no means an accurate index of the allergenic activity of an extract.

For these reasons, Cooke and Stull,²⁰⁵ in 1933, suggested standardization by determination of the *protein nitrogen* as the measure of

protein content. They define a protein nitrogen unit as one that represents 0.00001 mg. of protein nitrogen, as estimated by precipitation of the albumin fraction with phosphotungstic acid. However, Coca,²⁰³ Bowman,²⁰⁶ and others were unable to find any correlation between the activity of the extract and the protein nitrogen content.

Coca²⁰⁷ redefined the Noon unit chemically as the quantity of pollen extract that contains 0.00001 mg. of total nitrogen (Coca-Noon unit). The objection to this method is again that the total nitrogen determination does not necessarily bear a relationship to the amount of active material.

These numerous methods of estimating the antigenic properties of pollen extracts obviously tend to create confusion. The general opinion is that there is no true relationship between any nitrogen determination and the biologic activity of the extracts. Arbesman and Eagle²⁰⁸ reported the ratio of the antibody-neutralizing activity of four similar ragweed pollen extracts—prepared in 1939, 1937, 1933, and 1929, and then stored at temperatures of from 4 to 8 C.—as found to be, in respective order, 100:16:4.5:1.2, indicating a fairly rapid deterioration. Despite the wide differences in the biologic activities of these four extracts, their protein nitrogen contents and their ratios of protein nitrogen to total nitrogen were identical. These authors also demonstrated that the protein nitrogen content is an unreliable measure of the biologic activity of pollen extracts by comparing the results obtained by direct anaphylactic procedures with those obtained by immunologic tests, such as passive transfer (Arbesman and Eagle²⁰⁹). The studies of Stier et al.^{209a} likewise indicate that neither the protein nitrogen unit nor the total nitrogen unit is an adequate measure of potency, as well as showing that the nature of the extracting fluid employed is of considerable importance. In other words, a pollen extract having a low protein nitrogen content may be high in antigenic activity, and vice versa. We, together with many others,

²⁰² BOWMAN, K. L. *ibid.* 5: 341, 1934.

²⁰³ COCA, A. F. *ibid.* 5: 345, 1934.

²⁰⁴ ARBESMAN, C. E., and EAGLE, H. *ibid.* 11: 15, 1939.

²⁰⁵ STIER, R. F. E., McNEIL, A. L., and ERNSDORFF, J.: *Ann. Allergy* 3: 401, 1945.

²⁰² NOON, L. *Lancet* 1, 1572, 1911.

²⁰³ COCA, A. F.: *J. Allergy* 4: 3-4, 1933.

²⁰⁴ COOKE, R. A.: *Laryngoscope* 25: 108, 1915.

²⁰⁵ Idem and STULL, A.: *J. Allergy* 4: 87, 1933.

therefore prefer the weight by volume standardization in combination with the original pollen unit system of Noon

Table 43 presents a comparison of all the unit systems discussed above

Recently, Rockwell²⁰⁰⁹ holding that the other methods are unsatisfactory introduced the molar standardization of ragweed pollen extracts For this purpose two determina-

est dilution of antigen that elicits in pollen sensitive individuals either a positive skin reaction or a reaction of arbitrarily chosen size This method was sharply criticized as being of little or no value as a measure of biologic activity although it has been applied with more success to dust and other extracts Another method is the complement fixation technic using rabbit antisera which is

TABLE 43—Comparison of Unit Values of Pollen Extracts (Tuft¹⁴⁸)

Units	Dosage Range	Comparative Values			
		Pollen Units	Total Nitrogen	Protein Nitrogen Units	Dilutions
Pollen unit extractive from 0.001 mg pollen (Noon ²⁰⁰²)	1		0.000016	0.64	1 cc of 1:1,000,000
	10		0.00016	6.4	1 cc of 1:100,000
	100		0.0016	64.0	1 cc of 1:10,000
	1,000		0.016	640.0	1 cc of 1:1,000
	10,000		0.16	6,400.0	1 cc of 1:100
Total nitrogen Kjeldahl method (Cooke ²⁰⁰⁴)	0.00001	0.625		0.4	1 cc of 1:1,600,000
	0.0001	6.25		4.0	1 cc of 1:160,000
	0.001	62.5		40.0	1 cc of 1:16,000
	0.01	625.0		400.0	1 cc of 1:1,600
	0.1	6,250.0		4,000.0	1 cc of 1:160
Protein nitrogen 0.00001 mg of protein nitrogen (Cooke and Stull ²⁰⁰⁵)	1	1:625	0.000025		1 cc of 1:640,000
	10	15:625	0.00025		1 cc of 1:64,000
	100	156:25	0.0025		1 cc of 1:6,400
	1,000	1,562.5	0.025		1 cc of 1:640
	10,000	15,625.0	0.25		1 cc of 1:64
Weight of pollen per volume of extractive	1 cc of 1:1,000,000	1	0.000016	0.64	
	1 cc of 1:100,000	10	0.00016	6.4	
	1 cc of 1:10,000	100	0.0016	64.0	
	1 cc of 1:1,000	1,000	0.016	640.0	
	1 cc of 1:100	10,000	0.16	6,400.0	

Pollen unit extractive averages 0.000016 mg of total nitrogen

Total nitrogen is expressed in milligrams

Protein nitrogen equals total nitrogen (Kjeldahl) less nonprotein nitrogen (phosphotungstic acid method)

Protein nitrogen averages 40 per cent of total nitrogen

tions are necessary, total nitrogen and total free α amino nitrogen in the phosphotungstic acid precipitate. The real value of molar standardization can however be shown only by extensive clinical use of it.

Lastly, there are three other methods for the standardization of pollen extracts. The first is the *biologic*, using for the comparison of pollen extracts the determination of the high

promising but not immediately applicable to the assay of the activity of pollen extracts in human beings. The third method is determination of the *minimal concentration* of the extract that is necessary to neutralize a serum containing the homologous antibody. This method was suggested by Cooke and his associates²⁰⁰⁶ was further studied by Stull and

²⁰⁰⁶ COOKE, R. A., STULL, A., HERALD, S., and BARNARD, J. H. *J. Allergy* 6: 311, 1953.

Sherman,²⁰¹ and highly recommended by Arbesman and Eagle.⁶⁴

The confusion with regard to the standardization of pollen extracts is somewhat less formidable in practice, thanks to the fact that the manufacturers of the products offer their preparations in all useful units; therefore, the practitioner who is accustomed to calculating his extracts according to the Noon unit system, for example, does not encounter any difficulties. The situation is further clarified by the fact that the dilutions are usually prepared on a decimal proportional basis.

c) SPECIFIC THERAPEUTIC METHODS

(1) Parenteral Method

The specific parenteral therapy of hay fever comprises three different methods (preseasonal, coseasonal, and perennial) and two* routes of administration (subcutaneous and intracutaneous). Before discussing the various technics, it might be best to consider the question as to what criteria are available to determine how great the total dose of pollen extract should be in a given case, or what final dose must be reached in order to obtain a satisfactory therapeutic result. Treatment would be far more efficient if we possessed a procedure by which we could ascertain just when a hay fever patient has been "desensitized." One might logically suppose that the results of specific skin tests would serve as an indication of this, in that weakening of the reactions might be interpreted as the beginning of hyposensitization and the absence of reaction as evidence of complete hyposensitization.

Without going into the extensive literature on the subject, it may be said that opinions are sharply divided as to whether or not there is a decrease in the reactivity of the skin coincident with a decrease in the patient's specific hypersensitivity. Thus, Rackemann, Le-

vine, and Coca, and also Vaughan, have never seen such a decrease, while Colmes,²⁰³ Sherman, Stull, and Cooke,⁷⁶ and Harley⁶⁰² report that the reactions to intracutaneous tests are somewhat diminished after treatment in the majority of cases but that they almost never become negative. Using the scratch method, Pearson²⁰⁵ claimed that the reactions are nearly always markedly weaker or even negative after treatment. Moreover, according to Baldwin and Glaser,²⁰⁷ there are patients who improve even though the cutaneous responses remain practically unchanged, and others who do not improve in spite of the fact that the skin reactions are reduced in size. Summarizing the available evidence, it must be said that the results of skin tests with pollen extracts in treated hay fever patients are, in general, not a reliable indication as to whether an adequate dosage has been reached in the given case, or whether treatment should be continued. Accordingly, it is hardly necessary to persist with treatment in an attempt to obtain a negative skin test at any cost.

Preseasonal Method.—The term "preseasonal treatment" designates the method by which injections of pollen extracts are begun some twelve weeks prior to the hay fever season—early enough, therefore, to permit a graduated series of about twenty doses, as a rule, to be administered at intervals of from four to seven days, the last dose being given at about the beginning of the season. It is generally advisable, moreover, to continue the treatment throughout the season at weekly intervals with a reduced dose (three-fourths to two-thirds of the maximum quantity at first, and at the height of the season one-half or less depending on the patient's reaction).

TECHNIC. Before going into details, it should be stated as a general rule that the treatment for each patient must be highly individualized. The general principle is to administer to the patient the maximum amount of pollen extract that he is able to tolerate without severe local reactions or constitutional symptoms. The maximum dose—about 7,000 to 10,000 Noon units in the majority of cases, when the subcutaneous route is used—should be reached just before the onset of the season.

Patients should be classified into three groups, according to the results of intracutaneous tests, and then

²⁰¹ STULL, A., and SHERMAN, W. B. *Ibid.* 10: 190, 1939

* Three additional routes of administration may be only briefly mentioned here, since they are essentially of academic rather than of practical interest: (1) topical hyposensitization by local application of pollen extract to the nasal mucosa, in increasing concentrations, with an atomizer (Mackenzie,⁷⁴ Francis²⁰²), (2) electrophoretic introduction of pollen extracts into the skin (Abramson²⁰⁶), (3) intravenous injection of diluted pollen extracts (Lichtenstein²⁰⁴).

²⁰² FRANCIS, C. *Brit. M. J.* 1: 1263, 1938

²⁰⁶ ABRAMSON, H. A.: *J. Allergy* 12: 169, 1941

²⁰⁴ LICHTENSTEIN, M. R.: *Ibid.* 5: 230, 1934

⁷⁶ COLMES, A. *Ibid.* 3: 449, 1932

²⁰⁵ PEARSON, B. *Guy's Hosp. Rep.* 20: 55, 1940

²⁰⁷ BALDWIN, L. B., and GLASER, J. *J. Allergy* 8: 129, 1937.

be treated according to their relative tolerance (For these tests it is advisable to use glycerin free extracts since glycerin itself may elicit responses simulating strongly positive reactions.) For the very sensitive or A class the initial dose should be small the increase moderate and the maximum dose well below the average (see Table 44). It should be stressed however that this method of classification has no relation to the

If symptoms develop in spite of preseasonal hypo sensitization the patient should be given coseasonal treatment consisting of small doses preferably intracutaneously.

If the patient presents himself very late—for example only two or three weeks before the onset of the season—intensive preseasonal treatment or rapid hyposensitization can be carried out. Treatment is

TABLE 44—Subcutaneous Preseasonal Treatment of Hay Fever

Dose No	Class A Very Sensitive			Class B Average Sensitive			Class C Moderately Sensitive		
	Concentration of Extract in Noon Units	Dose Cc	Noon Units per Dose	Concentration of Extract in Noon Units	Dose Cc	Noon Units per Dose	Concentration of Extract in Noon Units	Dose Cc	Noon Units per Dose
1		0.10	1		0.05	5	vial no 2		
2	vial no 1	0.20	2	vial no 2	0.10	10	100 units per cc — dilution	0.15	15
3	10 units per cc = dilution	0.30	3	100 units per cc = dilution	0.20	20	1:10,000	0.30	30
4	1:100,000	0.50	5		0.35	35		0.60	60
5		0.80	8		0.60	60	vial no 3	0.10	100
6		0.12	12		0.10	100	1,000 units per cc — dilution	0.20	200
7	vial no 2	0.20	20		0.15	150	1:1,000	0.30	300
8	100 units per cc = dilution	0.30	30	vial no 3	0.25	250		0.45	450
9	1:10,000	0.50	50	1,000 units per cc = dilution	0.40	400		0.70	700
10		0.80	80	1:1,000	0.55	550		0.10	1,000
11		0.15	150		0.80	800		0.15	1,500
12	vial no 3	0.20	200		0.10	1,000		0.20	2,000
13	1,000 units per cc = dilution	0.30	300		0.15	1,500		0.25	2,500
14	1:1,000	0.40	400		0.25	2,500	vial no 4	0.30	3,000
15		0.55	550		0.30	3,000	10,000 units per cc = dilution	0.40	4,000
16		0.70	700	vial no 4	0.40	4,000		0.50	5,000
17		0.85	850	10,000 units per cc = dilution	0.45	4,500	1:100	0.60	6,000
18	vial no 4	0.10	1,000		0.50	5,000		0.70	7,000
19	10,000 units per cc = dilution	0.12	1,200	1:100	0.55	5,500		0.80	8,000
20	1:100	0.15	1,500		0.60	6,000		0.90	9,000
								1.00	10,000

Class A marked reaction to 0.1 cc. of 1:100,000 dilution of pollen extract intracutaneously

Class B marked reaction to 0.1 cc. of 1:10,000 dilution intracutaneously

Class C reaction to 0.1 cc. of 1:100 dilution intracutaneously

The interval between injections should be three days at the beginning then five later seven days. The dosage indicated must be modified according to the patient's tolerance.

degree of clinical symptoms i.e. a class A patient may have milder hay fever symptoms than does a class C patient.

Despite the differences in relative tolerance and therefore in dosage between the three groups the clinical results are equally good provided the treatment is properly individualized. It must be granted however that as a general rule the higher maximal doses achieve the best results.

begun with daily subcutaneous injections at first as the stronger doses are reached the intervals between doses are lengthened to two days then toward the end of the treatment to three days depending on the degree of reaction. The controlling factor in this as in other methods of parenteral treatment is the local response. Dosage and the intervals between doses should be graduated in such a manner that the skin reactions are not much larger than 25 mm (1 inch) in diameter and

these should subside before the next injection is given. The results obtained with this method are often good, but the danger of evoking systemic manifestations is so great that it cannot be generally recommended.

Lastly, there is the "rush" desensitization method, suggested by Freeman,²⁹¹ and employed either during the two to five days preceding or at the very beginning of the hay fever season. The technic consists in giving injections of increasingly larger and stronger doses of the antigen every two hours (for details, see p. 214). This approach has not been accepted for the reason that almost all patients suffer from more or less severe shock symptoms. In any event, it is to be administered only in a hospital and under the supervision of a physician specially trained in the technic. Waldbott and Ascher²⁹² have reported, moreover, that this method not uncommonly brings on severe late reactions, often appearing after many hours. (Parenthetically it may be stated that in the writers' opinion this treatment is one of deallergization based on slight macroshocks, rather than hypsensitization.)

Contra-indications for pollen injections are severe acute or chronic diseases, such as nephritis, cardiac disease or decompensation, diseases of the blood, thyrotoxicosis, and advanced pregnancy. (The present writers therefore employ oral therapy during pregnancy.) Furthermore, it is inadvisable to increase the dose for women during the period from three days before to the end of each menstruation.

On the basis of clinical and immunologic studies, chiefly of the blocking or thermostable antibody, Loveless²⁹³ has suggested that short preseasonal "booster" courses of therapy may be given in place of the usual regimen, in seasons subsequent to the first season of treatment. Generally satisfactory results were obtained when a total of 10,000 protein nitrogen units were administered during an average of 68 visits (more than one injection being given at half-hour intervals at some visits) over a period of twenty-six days. Threshold tests of conjunctiva and skin prior to the course of treatment gave some indication as to potential generalized reactions, and at the conclusion of the course, as to the adequacy of protection. In general, the higher the threshold of conjunctival reaction to tests with liquid pollen extract, the better the subsequent response to specific therapy, and according to Loveless²⁹³ this method gives promise of serving as a guide to the amount of specific treatment required by a hay fever case. Less well

correlated, but still somewhat indicative of the clinical response, was the determination of the thermostable antibody titer. The authors warn that this type of treatment is still in the experimental stage and not for general application. The booster principle should be applied with discretion, and only for patients whose tolerance is well known. When threshold tests prior to therapy show high levels of sensitivity, initial doses should be correspondingly low.

Cohen and Friedman²⁹⁴ prepared mixtures of pollen extract and thermostable antibody which were immunologically approximately neutral (containing less than 100 phosphotungstic acid precipitate units of free antigen per cc). The antibody was obtained by repeated subcutaneous injections of pollen extract into normal nonsensitive individuals, the globulin being separated by dialysis fractionation, and then lyophile-dried and titrated. These mixtures stimulated antibody production in both normal and pollen-sensitive subjects and had the advantage that they could be given in large dosage to sensitive patients without systemic reactions.

Coseasonal Method.—This technic has two indications: it is advantageous in the case of those patients who report too late for the institution of preseasonal therapy, and for those who have received either no benefit or inadequate protection from the preseasonal treatment, whether or not the latter was carried to completion. Introduced in 1921 by Walker, the coseasonal method was perfected by Vaughan²⁹⁵ for application by the subcutaneous route, and by Phillips²⁹⁶ and Hansel²⁹⁷ for use by the intracutaneous route.

The coseasonal differs from the preseasonal method in two principal points: (1) only small quantities of pollen extract are employed, and (2) injections are administered daily (or every other day).

TECHNIC. In the event that the patient has not previously been tested or treated, the degree of his hypersensitiveness must first be very carefully determined. If his hypersensitiveness is found to be about average, and if the subcutaneous method is to be employed, treatment is begun with 0.1 cc. of a 1:10,000 dilution (10 Noon units). If the patient then shows

²⁹¹ COHEN, M. R., and FRIEDMAN, H. J. *J. Allergy* 16: 121, 1945.

²⁹² PHILLIPS, E. W. *Ibid.* 5: 29, 1933.

²⁹³ HANSEL, F. K. *Ibid.* 12: 457, 1941.

²⁹⁴ LOVELESS, M. H. *J. Ann. Allergy* 3: 333, 1945.

marked improvement the dosage is not increased if not each dose is cautiously increased by 0.1 cc until a dose of 100 units is reached. As soon as an improvement of some 75 per cent is observed injections are given only every second or third day and subsequently only weekly. Occasionally when severe hay fever symptoms are present at the time of injection it is advisable to include 0.1 cc of 1:1000 epinephrine in the same syringe.

Hansel²⁰¹ has most emphatically recommended the intracutaneous route. Both Tuft¹⁴² and the present writers have obtained noteworthy results with this method.

TECHNIC. Prior to treatment the skin sensitivity of the patient is determined by successive intracutaneous tests with dilutions ranging from 1:1000 to 1:10000. If a positive whealing reaction as large as 15 mm in diameter is noted in response to any dilution no further tests are made at the initial sitting. Treatment is usually started with 0.01 cc of the 1:10000 dilution. Subsequent doses should be administered first every day, later every two, three or five days or at longer intervals according to the duration of the relief obtained. Occasionally injections twice daily if feasible will be found to give better results at the outset. The amount of each injection should be increased by 0.01 cc as shown in Table 45. The average size of a wheal that produces satisfactory relief varies from 20 to 25 mm in diameter. For patients in whom a wheal of about 15 mm develops from an injection of 0.01 cc of the 1:10000 solution treatment is begun with 0.02 cc of the same dilution and increased according to the schedule, the reactions and the relief of symptoms. Likewise for patients in whom a 15 mm wheal is produced with the 1:1000 dilution the dose is begun with 0.02 cc and continued in the same manner. In patients of less than average sensitivity the treatment may be begun with the 1:1000 dilution in doses up to 0.05 cc, after which the 1:100 dilution is used.

It is interesting to note that systemic reactions to coseasonal therapy are rare, when they do occur, they appear promptly and are therefore readily controlled. Like the Asthma Clinic of St. Mary's Hospital,²⁰² London, the present writers have found it satisfactory to teach self inoculation to intelligent and reliable patients who require daily intracutaneous injections, and who are unable to come to the office or clinic as frequently as this necessitates. For this treatment, strict and limited orders, for no more than one week ahead, must be given. The patient should also receive instructions as to how to give himself epinephrine, if and when necessary. There can be no

more objection to this procedure, provided the patient faithfully reports to his physician once a week than in allowing a diabetic to give himself insulin.

Perennial Treatment.—The outstanding disadvantage of the preseasonal and coseasonal methods is that they are discontinued at the end of the hay fever season. As a result, the tolerance that is attained in the course of treat-

TABLE 45.—Intracutaneous Coseasonal Treatment of Hay Fever

Dose No.	Concentration of Extracts			Total N. trogen per Dose (Mg.)	Noon Coca Uts per Dose
	Dilution	Mg. N. trogen per 1 Cc.	Dose Cc.		
1	1:100,000	0.0001	0.01	0.000001	0.1
2			0.02	0.000002	0.2
3			0.03	0.000003	0.3
4			0.04	0.000004	0.4
5			0.05	0.000005	0.5
6	1:10,000	0.001	0.01	0.00001	1.0
7			0.02	0.00002	2.0
8			0.03	0.00003	3.0
9			0.04	0.00004	4.0
10			0.05	0.00005	5.0
11	1:1,000	0.01	0.01	0.0001	10.0
12			0.02	0.0002	20.0
13			0.03	0.0003	30.0
14			0.04	0.0004	40.0
15			0.05	0.0005	50.0
16	1:100	0.10	0.01	0.001	100.0
17			0.02	0.002	200.0
18			0.03	0.003	300.0
19			0.04	0.004	400.0
20			0.05	0.005	500.0

ment is lost again after a few weeks and must be painstakingly increased the following year. To Stewart²⁰³ must go the credit of being the first to recommend continuation of the treatment throughout the year, in order to maintain the antibody titer of the blood at a high level all the time. This method was then developed by Brown,²⁰⁴ Vander Veer and his associates,²⁰⁵ and Kahn,²⁰⁶ and now has a large following. The present writers employ the perennial

²⁰² STEWART Z. W. J. Iowa M. Soc. 16: 277, 1926.

²⁰³ BROWN A. J. Immunol. 13: 273, 1927.

²⁰⁴ VANDER VEER A. J., COOKE R. A. and SPAIN W. C. Am.

J. M. Sc. 174: 101, 1927.

²⁰⁵ KAHN I. S. J. Lab. & Clin. Med. 13: 17, 1927.

method wherever possible, especially because of the definite possibility of establishing a state of permanent insensitiveness after several years of such treatment, as shown by Sberman and Stull³²⁵—a process that the writers prefer to regard as one of deallergization. The following additional advantages of the perennial method have been reported: (1) avoidance of intensive treatment (relatively large dosage administered during a short time) as in the pre-seasonal method, hence making it more convenient for the patients, and supposedly leading to fewer constitutional reactions, (2) fewer injections; (3) the possibility of beginning at any time of the year, (4) better results; (5) frequently better general condition throughout the year, since the patient's threshold of tolerance to other allergens, particularly bacterial antigens, is elevated (metallergic effect).

On the other hand, Vander Veer²⁰⁴⁷ stresses the fact that the perennial method (although admittedly giving results that are some 10 per cent better) involves certain disadvantages. An appreciable percentage of patients fail to report with the required regularity, so that the physician is forced to return, time and again, to smaller and weaker doses. Furthermore, as Peshkin²⁰⁴⁸ has pointed out, systemic reactions are not uncommon, sometimes after doses previously well tolerated, and even when the injection does not elicit a positive local reaction.

TECHNIC. Perennial treatment can be instituted at any time of the year with the doses shown in Table 44, according to the patient's cutaneous sensitivity. Or it may constitute simply a continuation of therapy that was begun preseasonally or coseasonally. At the conclusion of the hay fever season, the dose last given is maintained and repeated at intervals of two weeks throughout the year, if possible, with no less than 4,000 Noon units per dose in an average case, unless the patient's systemic or local responses indicate the desirability of a different amount or interval. Approximately five weeks before the onset of the hay fever season, the quantity is increased at weekly intervals to the maximum level. Then, during the season proper, the dosage is decreased, if necessary, since the body is also called upon to handle the additional quantities of pollen inhaled from the air, but injections are still continued at intervals of about seven days.

When one is obliged to change to a newly prepared extract, it is advisable to mix it with the old extract for the first few injections, to avoid possible overdosage: one part of the new extract mixed with two parts of the

old, for one injection, and two parts of the new with one part of the old for the next. If no reactions ensue, the new extract alone may be given subsequently.

There is a considerable divergence of opinion as to the quantity of the single dose to be injected. Rackemann²⁰ favors the so-called "optimal dose," which must be established empirically for each patient, and which must definitely not be too large. Brown,²⁰⁴⁹ on the other hand, states emphatically that he has achieved excellent results and permanent hypsensitization with maximal doses of pollen (as much as 1 to 2 cc. of a 10 per cent pollen extract)—the so-called maximum dosage pollen therapy. Authorities also disagree on the question of the best interval. A period of four weeks seems inappropriate, for, according to Vaughan, Nelson, and others, systemic reactions appear with relative frequency under this regimen. The present writers prefer a biweekly maintenance interval.

Since the sensitivity tends to diminish as the years go by, it is advisable to "classify" the patient every year, for increased dosage may be necessary. In the second year of perennial treatment, intervals up to three weeks can, as a rule, be permitted.

Since quite a few patients have two or even three different pollination seasons to cope with, the physician is confronted with the question as to whether combined or separate extracts should be used. Some authors run these patients up to the point of maximum tolerance by using two or three extracts separately, and then combine these in whatever proportions are indicated by the patient's capacity. For example, if the patient can take 0.6 cc. of a 1:100 dilution of the pollens of grasses and 0.4 cc. of a 1:100 dilution of the ragweeds, a 10 cc. vial would have to be made up of 6 cc. of the grasses and 4 cc. of the ragweeds.

Other authors, including the present writers, prefer giving the grass and the ragweed pollens separately, thus making a more intensive course possible. This is desirable, for example, with the grasses alone for the thirty days prior to the usual date of onset of the attack; the same applies to the treatment just prior to the pollination of the ragweeds. The use of two different extracts also permits one to cut down, if necessary, the amount of the grass extract

²⁰⁴⁷ VANDER VEER, A. J. *Allergy* 7: 578, 1936.

²⁰⁴⁸ PESHKIN, M. M. *Ibid.* 7: 477, 1936.

²⁰⁴⁹ BROWN, G. T. *Ibid.* 6: 86, 1934.

given during the usual season, and of the ragweed extract given during the period of ragweed pollination, in order to compensate for the amount of pollen the patient inhales at that time

Reactions—There is no allergic treatment that is followed by so many local and systemic reactions as is pollen therapy for hay fever. Although these manifestations are rarely dangerous, the physician must always be prepared to combat them with 1:1,000 epinephrine (see p. 225). There are three types of reactions that may accompany or follow injection of pollen extracts: (1) There may be immediate pain or discomfort at the site of injection; this may be due to the volume of the dose (e.g., if over 0.5 cc) or to the nature of the menstrium, especially if it contains glycerin. (2) Local symptoms appearing some time after injection are due to the ensuing antigen-antibody reaction. They may be of the immediate type, occurring after twenty minutes and consisting of swelling generally not greater in diameter than 25 mm (1 inch), erythema, and itching; these symptoms usually disappear after a few hours, without causing more than slight discomfort. However, the injection may be followed by a delayed reaction, characterized by rather large swelling, induration, and tenderness that may even involve the whole arm and persist for twenty-four to thirty-six hours. Such a reaction is an indication that the dose was too large and should be reduced, or divided into two doses to be administered at different sites. (3) Systemic reactions appear not too rarely at some time during the course of treatment (in 13 per cent of cases, according to Vander Veer,²⁶⁴⁷ and in 11.7 per cent according to Furstenberg and Gay.²⁶⁴⁸) Waldbott²⁶⁵¹ reported the incidence of these reactions in a large series of pollen extract injections to be about 1:250 injections, chiefly due to overdosage. They commence with sneezing, coughing, or itching in the nose, ears, and palms of the hands, followed by erythema, urticaria, angioneurotic edema, tachycardia, or asthma. Diarrhea, vomiting, headaches, fall in body temperature, and even loss of consciousness occur in instances of this kind. These ana-

phylactic reactions can be promptly managed by immediate administration of epinephrine and other measures. However, a few isolated instances of anaphylactic death have been observed (Lamson²⁶⁴⁹, Waldbott,²⁶⁵¹ Dahl,²⁶⁵⁴ Vance and Strassmann¹⁸⁵⁵).

Among the more unusual forms of untoward reactions, the following may be mentioned: Francis²⁶⁵⁰ and Hansen⁹⁹ reported cases of abortion following constitutional reactions; Cooke reported abdominal and uterine cramps, as well as vaginal bleeding without abortion. Squier and Madison²⁶⁵⁵ saw a patient who had severe menorrhagia during the course of pollen therapy. She was found to have a definite drop in thrombocytes and leucocytes, and a rise in eosinophils, after each injection. Her menorrhagia cleared up on the termination of pollen therapy. Severe polyneuritis resulting from pollen therapy was described by van Leeuwen, flare up of a dormant arthritis, by Wessely and Koerbel, and anaphylactic joint reactions were seen by the senior author. Deissler²⁶⁵⁶ observed the sudden precipitation of pulmonary edema in a patient with a compensated rheumatic double mitral lesion, as a result of an overdosage of pollen antigen. The patient's cardiac reserve was lowered for some time thereafter. Francis²⁶⁵⁷ described a case of localized atrophy of the subcutaneous fat from repeated injections of grass pollen extract in a diabetic who had received no insulin for over a year. All such occurrences must be rare.

The most common causes of constitutional reactions are (1) extreme hypersensitiveness in some individuals, (2) too large an initial dose, (3) too large an increase in dosage, (4) faulty selection of dosage, usually as a result of ignoring the size of previous local reactions, (5) errors in dosage, particularly if two or more injections are given at the same time, (6) change from an old to a freshly prepared extract, (7) improper administration (e.g., faulty technic, such as an inadvertent intravenous injection or back seepage²⁶⁵⁸), (8) simultaneous absorption of unpredictable amounts of pollen

²⁶⁴⁷ LAMSON R. W. *ibid.* 93:1775, 1929.

²⁶⁴⁸ WALDBOTT G. L. *ibid.* 96:1848, 1931.

²⁶⁴⁹ DAHL B. *Klin. Wochenschr.* 16:491, 1917.

²⁶⁵⁰ SQUIER T. L. and MADISON F. W. *J. Allergy* 8:143, 1937.

²⁶⁵¹ DESSLER K. J. *Ann. Allergy* 2:299, 1944.

²⁶⁵² FRANCIS N. *ibid.* 2:314, 1944.

²⁶⁴⁸ FURSTENBERG F. F. and GAY L. N. *Bull. Johns Hopkins Hosp.* 60:412, 1937.

²⁶⁵¹ WALDBOTT G. L. *J. A. M. A.* 128:1226, 1945.

from the air during the hay fever season; and (9) absorption of food or inhalant allergens other than pollen, to which the patient is sensitive.

In addition to careful attention to all the above possibilities, the following precautions are always advised in giving pollen injections. On the day of treatment the patient should not eat foods to which he is sensitive. The site of injection should be carefully selected to avoid visible veins, and to permit the later application of a tourniquet, if necessary. Before each injection the plunger of the syringe should be pulled back two or three times after insertion of the needle to observe for evidence of blood as a sign of accidental intravenous introduction. The patient should remain under observation for at least twenty minutes and observed for excessive local edema and the earliest manifestations of a systemic reaction. The management of constitutional reactions has been covered in the preceding chapter, and need not be repeated here.

It may be mentioned, however, that if small quantities of a concentrated solution (e.g., 0.2 cc of 1:100) cause systemic reactions, one may try the method of diluting it in the syringe with 0.8 cc. of isotonic saline solution. As a result, absorption is much slower and the mixture therefore often tolerated. After a reaction, no further pollen injections should be given for at least twenty-four to forty-eight hours, and the subsequent course of therapy should be appropriately modified.

Results of Specific Pollen Hyposensitization with Intra- or Subcutaneous Methods—Despite the numerous modifications of methods of treatment, dosage, route of administration, and pollen-extracting fluids, the chances of achieving a permanent cure are only fair. As Vaughan¹ rightly says: "It is safer to speak of relief than of cure in pollinosis." He estimates that no more than 7 per cent of all patients—after several years of treatment—become really symptom-free; and even some of these suffer recurrences after a number of years.

In the literature the statement is often seen that some 80 to 90 per cent are adequately relieved of their discomfort during the season. Anyone who has had the opportunity of treating a large number of hay fever patients, either in private practice or in the clinic, will regard

statements of this kind with some skepticism. Eyermann,²⁶⁵ in reiterating the known fact that the estimation of the results of hay fever therapy is particularly difficult, points out that the reports are based on the patient's evaluation, colored by the physician's enthusiasm, which in turn is influenced by his experience with other methods of treatment and his belief in the validity of the theory upon which the therapy is based. Confusion in the interpretation of individual therapeutic results will persist until (1) a laboratory test is developed which will indicate that the offending allergens no longer induce symptoms; (2) all reports include data on all other factors influencing the symptoms, such as meteorologic conditions, the degree of sensitivity, the additive effect of allergens other than pollen, the psychic reaction to discomfort, the irritant effect of intranasal therapy, auto-inoculation, and other personal factors; (3) reports include a comparable group of untreated or differently treated controls, and (4) the therapeutic results on the same patients are reported from year to year.

It must be admitted that many patients, for a variety of reasons, fail to adhere to the prescribed schedules, but even those who follow the treatment with perfect regularity do not always show sufficient improvement. However, it is true that one often succeeds in making the patient more comfortable, and, above all, in preventing development of the most distressing symptom—asthma.

In cases in which therapy is only partially successful, or in which it fails completely, the physician should consider the following factors very carefully, since the correction of any one of them may lead to prompt improvement.

1. *Faulty selection of pollen extract.* This is usually the result of inadequate preliminary testing. As pointed out in some detail on page 524, the patient should be tested with all the pollens in his zone and also with those of the plants growing in his immediate environment. In some instances slides must be exposed, and the pollen identified by a botanist. Furthermore, it must be remembered that cutaneous tests cannot always be depended upon, and must often be replaced or supplemented by nasal or ophthalmic tests.

²⁶⁵ EYERMANN, C. H. Letters, Internat. Congr. Club of Allergy, Series 8: 140, 1945.

2 *Improper administration of treatment* The importance of individualizing the treatment of each particular case cannot be stressed too emphatically. It should also be borne in mind that injection schedules are intended to serve only as more or less general guides and that strict adherence to any such program will often fail to bring satisfactory results. The errors belonging to this category are improper dosage for the individual injections, selection of incorrect intervals between injections and above all a maximum dose that is too weak or too strong. The error may also lie in the patient's failure to adhere to the prescribed schedule.

3 *Deterioration of extracts* This may be due either to faulty storage (extracts should be refrigerated) or to the age of the extract.

4 *Too massive exposure to pollen* Every patient should be told that the protection given by the injections may be overcome by exposure to too great a quantity of pollen. The writers have often observed patients who felt very well and wanted to see whether they were really cured and therefore deliberately lay down near pollinating plants or even sniffed pollen. These experiments always resulted in very severe attacks. The same is true of soldiers forced by military necessity to crawl through or sleep in fields during the season.

5 *Extreme hypersensitiveness to the injected pollen protein* Such susceptibility on the part of the patient may make it impossible to attain an adequate dose owing to unduly large local or even constitutional reactions.

6 *Effect of associated allergens* In an appreciable percentage of all hay fever patients there is an additional hypersensitiveness during the hay fever season to any of a great variety of substances such as house dust, face powder, flour, molds, rusts, perfumes, animal emanations, foods, nose drops and drugs. The associated allergens may act on the mucosa of the nose, bronchi or gastrointestinal tract and less commonly on the skin. The unearthing of these additional antigens must not be based merely on skin reactions but the physician must rely essentially on a painstaking history and appropriate exposure trials, elimination diets and the like.

7 *Influence of nonspecific factors* Like many patients suffering from other allergic diseases, a not inconsiderable number of hay fever patients manifest—during the season—

a pathergy (nonspecific sensitivity) to all manner of influences to which they are normally exposed. These include mechanical or chemical irritation of the nasal mucosa (dust, powder, shreds of cotton, strong odors to tobacco or other smoke) and the irritating effects of heat or cold (especially sudden changes from hot to cold or vice versa) or of sunlight.

(2) Oral Methods

The injection methods have a number of distinct disadvantages: (a) persons who are needle shy, especially children, often refuse to submit to treatment; (b) individuals who are very busy or who travel a great deal or who live at a distance from medical centers find it most inconvenient to visit the physician twenty or more times; (c) many cannot afford to pay for such treatment; (d) there is always a possibility of systemic reactions or shock resulting from injections, although an experienced therapist can reduce the number and severity of these reactions; they cannot be entirely avoided.

The most successful alternative to the hypodermic injection method has been the administration of pollen by mouth. Numerous investigators have reported encouraging results with this approach. Among the advantages of the oral method, the following may be mentioned: its simplicity, the absence of pain, therefore making it a method especially suitable for children, a wider margin of safety and the availability of treatment under unusual conditions (e.g. for those who are unable to make frequent visits to the physician's office or the clinic). On the other hand, in its present stage of development, the oral method of specific pollen treatment gives a lower percentage of satisfactory results than does the hypodermic method and a higher percentage of complete failures and rather often causes gastrointestinal discomfort.

It is of historical interest that as early as 1890 the homeopaths employed a tincture of fresh flower heads and young shoots for treatment of hay fever (Wightman²⁵⁸). Curtis²⁶⁰ in 1900 was the first physician to administer an aqueous extract of flowers and pollen orally and he claimed satisfactory results. Twenty

²⁵⁸ W. WIGHTMAN, H. B. *Transactions of the British Medical Association*, 1890, 1, 11, and Gay, L. N. *J. A. C. G.* 12, 605, 1911.

²⁶⁰ CURTIS, H. H. *M. News (New York)* 77, 16, 1900.

two years later, Touart²⁶⁶¹ tried oral administration with tablets containing 0.1 mg of the protein of pollens. Since then, many investigators, including Black,^{2662, 2663} Thommen,²⁶⁶⁴ Gatterdam,²⁶⁶⁵ Stier and Hollister,²⁶⁶⁶ McGrew,²⁶⁶⁷ Rockwell,²⁶⁶⁸ Bohner,²⁶⁶⁹ Alperstein,²⁶⁷⁰ Schwartz,²⁶⁷¹ Iliff and Gay,²⁶⁷² and Thiberge^{2673, 2674} have reported good or satisfactory results. On the other hand, Bernstein and Feinberg,²⁶⁷⁵ Forman,²⁶⁷⁶ Zeller,²⁶⁷⁷ and a cooperative group under the direction of Feinberg²⁶⁷⁸ hold the results of oral pollen therapy to be definitely inferior to those obtainable by parenteral administration of pollen extract.

Since, as mentioned above, oral pollen therapy quite often induces distressing gastrointestinal symptoms, the senior author introduced oral treatment with digested pollen, the so-called pollen propeptan (see case history, p. 518, and Figs. 246, 247). By digesting the pollen proteins with hydrochloric acid, pepsin, and trypsin he²⁶⁷⁹ succeeded in obtaining preparations which, while free of native protein, retain their type-specificity. They are composed chiefly of proteoses and peptones. It will be seen that the same reasoning was followed here as in the preparation of the food propeptans.

Recently Urbach, Jaggard, and Crisman²⁶⁷⁸ succeeded in protecting guinea pigs so highly sensitized to ragweed or timothy pollen that they died when exposed to inhalation of pollen mist, by oral preadministration of the respec-

tive pollen propeptans. Under appropriate conditions as to quantity and time these pollen propeptans protect guinea pigs against otherwise fatal anaphylactic reactions or most severe bronchial asthma. The illustrations show the difference between the uterine reaction (Schultz-Dale test) of a sensitized but unprotected animal (Fig. 261A) and that of one treated orally with pollen propeptan (Fig. 261B). FIGURES 261C and 261D contrast the condition of the lungs of such animals in the lung perfusion test. It is also pertinent to note that preadministration of specific pollen digests by the bronchial or intravenous routes will protect highly sensitized guinea pigs against approximately five times the lethal dose of ragweed or timothy pollen extract.

With respect to the mechanism underlying oral pollen therapy, opinions are sharply divided. The majority of authors consider the mechanism to be a form of hyposensitization. The present writers, on the other hand, are of the opinion that a skeptophylactic mechanism is involved and regard the oral method as falling in the category of deallergization (see p. 212).

A number of authors (C. Bernstein and Kirsner; T. B. Bernstein and Feinberg; and London) were unable to demonstrate enteral absorption, even when doses as large as 5 Gm. (5,000,000 Noon units) were administered orally. These examinations were carried out on healthy individuals. We must assume on the other hand, however, that hay fever patients absorb pollen by way of the gastrointestinal tract, since many patients present allergic reactions, such as urticaria, slight hay fever, slight asthma, and gastro-intestinal discomfort, after ingestion of pollen preparations. Moreover, Black²⁶⁶² had previously demonstrated an appreciable amount of the active substance of the pollen in the blood serum and urine of hay fever patients who had taken pollen extracts orally, and Levin and Shulsky²⁶⁸⁰ presented evidence, by serologic methods, that ragweed pollen is absorbed in the case of children by way of the gastro-intestinal tract. More recently, Thiberge²⁶⁷⁹ found that locally sensitized skin sites in 14 normal subjects showed positive reactions in 4, and a doubtful reaction in 1, following ingestion of

²⁶⁶¹ TOUART, M. D. J. New York M J 116: 190, 1922

²⁶⁶² BLACK, J. H. J. Lab & Clin Med 12: 1156, 1927

²⁶⁶³ Idem J Allergy 10: 136, 1939

²⁶⁶⁴ GATTERDAM, E. A. Southwestern Med 18: 180, 1934

²⁶⁶⁵ STIER, R. F. E., and HOLLISTER, G. Northwest Med. 36: 166, 1937

²⁶⁶⁶ MCGREW, G. D. Mil Surgeon 89: 371, 1937

²⁶⁶⁷ ROCKWELL, G. E. Ohio State M J 34: 784, 1938.

²⁶⁶⁸ BOHNER, C. B. J. Indiana M A 31: 279, 1938

²⁶⁶⁹ ALPERSTEIN, B. B. J. Allergy 11: 495, 1940

²⁶⁷⁰ SCHWARTZ, S. C. J. Lab & Clin Med 25: 366, 1940

²⁶⁷¹ ILIFF, E. H., and GAY, L. N. Bull Johns Hopkins Hosp 70: 335, 1942

²⁶⁷² THIBERGE, N. F. New Orleans M & S J 94: 390, 1942

²⁶⁷³ Idem South M J 38: 521, 1945

²⁶⁷⁴ BERNSTEIN, T. B., and FEINBERG, S. M. Arch Int Med 62: 297, 1938

²⁶⁷⁵ FORMAN, J. Ohio State M J 35: 527, 1939.

²⁶⁷⁶ ZELLER, M. J. Allergy 10: 579, 1939

²⁶⁷⁷ FEINBERG, S. M., FORMAN, J. L., LICHTENSTEIN, M. R., PARNOS, E., RAPPAPORT, B. Z., SHELDON, J., and ZELLER, M. J. A M. A 115: 23, 1940

²⁶⁷⁸ URBACH, E., JAGGARD, G., and CRISMAN, D. W. Ann Allergy (in press).

²⁶⁷⁹ THIBERGE, N. F. J. Allergy 15: 298, 1944.

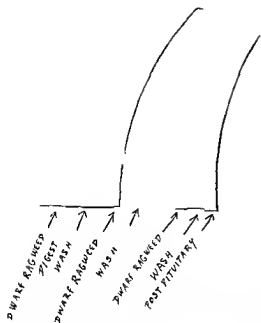


FIG 261A UTERINE REACTION (SCHULTZ DALE TEST) OF SENSITIZED BUT UNTREATED GUINEA PIG

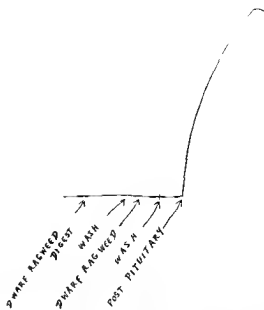


FIG 261B UTERINE REACTION (SCHULTZ DALE TEST) OF SENSITIZED GUINEA PIG ORALLY TREATED WITH POLLEN PROPEPTAN



FIG 261C RESULT OF LUNG PERFUSION TEST OF SENSITIZED BUT UNTREATED GUINEA PIG

Left lung of sensitized animal shows maximal inflation indicating that the lung is highly allergic. Right lung of non sensitized guinea pig for comparison

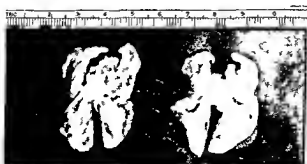


FIG 261D RESULT OF LUNG PERFUSION TEST OF SENSITIZED GUINEA PIG ORALLY TREATED WITH POLLEN PROPEPTAN

Left lung of sensitized animal which had been given oral treatment with pollen propetian shows no reaction. Right lung of non sensitized guinea pig for comparison

only 0.048 Gm. ($\frac{3}{4}$ grain) of pollen in enteric-coated pills. Employing a similar method but 5 Gm. of ragweed pollen as well as the simultaneous administration of alkalis in subjects without gastric hypoacidity, Hecht and his co-workers⁷⁹⁵⁰ obtained positive reactions in 16 of 22 subjects. According to Rockwell,⁷⁹⁵¹ the pollen antigen appears in appreciable quantities in the blood of rabbits fifteen minutes after oral administration.

TABLE 46—*Dosage Schedule for Preseasonal and Perennial Oral Treatment with Whole Pollen Preparations*

Day	Dose	Units	Number of Capsules and Color	Vial
1	1	500	1 pink	6 pulvules
4	2	1,000	2 pink	
7	3	1,500	3 pink	
11	4	2,000	1 yellow	6 pulvules
14	5	4,000	2 yellow	
18	6	6,000	3 yellow	
21	7	8,000	1 green	6 pulvules
25	8	16,000	2 green	
28	9	24,000	3 green	
32	10	30,000	1 brown	6 pulvules
33	11	30,000	1 brown	
39	12	30,000	1 brown	
42	13	30,000	1 brown	
46	14	30,000	1 brown	
49	15	30,000	1 brown	4
53	16	60,000	1 clear	40 pulvules
55	17	120,000	2 clear	
57	18	120,000	2 clear	
58	19	120,000	2 clear	
59 on	20 on	120,000	2 clear (or more)	5

In oral therapy as in parenteral treatment, one must differentiate between the preseasonal, coseasonal, and perennial forms.

It must be stated, first of all, that wherever possible the oral preparations should be individually compounded in accordance with the outcome of tests on the patient. At present, there are available two types of preparations:

whole pollen mixtures (Eli Lilly and Company, Indianapolis, G. H. Sherman, Inc., Detroit), and pollen propeptans, derived by digestion of pollens with hydrochloric acid and enzymes (Dalare Associates, Philadelphia 3, Pa.).

Tables 46 and 47 present suitable dosage schedules for preseasonal, perennial, and coseasonal therapy of hay fever with whole pollen preparations.

We personally prefer treatment with pollen propeptans, i.e., enzyme-digested pollen proteins. It has generally been found that the best results are obtained with perennial oral

TABLE 47—*Dosage Schedule for Coseasonal Oral Treatment with Whole Pollen Preparations*

Day	Dose	Units	Number of Capsules and Color	Vial
1	1	500	1 pink	1
2	2	1,000	2 pink	
3	3	1,500	3 pink	
4	4	2,000	1 yellow	2
5	5	4,000	2 yellow	
6	6	6,000	3 yellow	
7	7	8,000	1 green	3
8	8	16,000	2 green	
9	9	24,000	3 green	
10 to 15	10 to 15	30,000	1 brown	4
16 on through season	16 and on	60,000 to 120,000	1 clear or more	5

treatment. Moreover, whenever possible, we prescribe an individualized pollen propeptan mixture—the formula being based on the patient's known hay fever season and on the results of scratch, intracutaneous, nasal, or conjunctival tests, with due regard for the anticipated degree of exposure to particular pollens.

The following two prescriptions provide examples of how the proportions of the various pollens are selected for a particular case. For instance, if a patient reacts strongly to giant and dwarf ragweed, moderately to cocklebur, and slightly to goldenrod and dahlia, a pre-

⁷⁹⁵⁰ HECHT, R., MOSKO, M. M., LEVIN, J., SCHLESINGER, M. B., and BAER, R. L. *ibid.* 15: 9, 1944

⁷⁹⁵¹ ROCKWELL, G. E. *J. Lab. & Clin. Med.* 27: 228, 1941

scription such as the following may be employed. The species and percentages are of course, varied according to the results of the tests and the degree of exposure.

℞ 100 capsules each containing 100 000 pollen propeptan units along with 0.01 Gm of glycyrrhiza according to the following formula.

	Percentage
Giant ragweed	40
Dwarf ragweed	40
Cocklebur	10
Goldenrod	5
Dahlia	5

In a typical grass pollen hay fever case, manifesting moderate reactions to the first three pollens listed below, and mild reactions

with the dates proportionately earlier will be suitable for hay fever due to tree pollens. These schedules are intended of course only as guides and must be adjusted to suit the needs of the individual case. The treatment must be begun about six weeks before the season starts. If the patient is gastro-intestinally sensitive, or if allergic reactions occur, deallergization must be attempted at a much slower rate. Much larger doses are given orally than hypodermically, evidently because only a small portion is absorbed. This is the reason why a small amount of glycyrrhiza, a saponin that promotes intestinal absorption (see p. 47), is added to each capsule. Since the beneficial effect of each dose lasts at least

TABLE 48—*Dosage Schedule for Preseasonal Oral Treatment with Weed Pollen Propeptan for Adults*

Date*	Dosage	Total Daily Dose pollen propeptan units
July 1-31	1 capsule a day	100 000
August 1-14	1 capsule twice a day	200 000
August 15-31	1 or 2 capsules three times a day depending on symptoms	300 000-600 000
September 1-end of season	2 or 3 capsules three times a day depending on symptoms	600 000-900 000

Each capsule contains 100 000 units of pollen propeptan. One unit of pollen propeptan is one microgram of specific pollen digest.

* Dates given are suitable for fall hay fever throughout the northeastern section of the United States but must be appropriately modified where season differs significantly.

to the remaining three, the prescriptions might read:

℞ 100 capsules each containing 60 000 pollen propeptan units along with 0.01 Gm of glycyrrhiza according to the following formula.

	Percentage
June grass	20
Timothy	20
Orchard grass	20
Red top	15
English plantain	15
Fescue	10

Preseasonal Oral Treatment—Preseasonal treatment should be instituted with daily dosage about six weeks before the onset of the season.

In the average fall case, the patient is instructed to follow the schedule given in Table 48. For grass pollen cases Table 49 provides the necessary information. A similar schedule

in the beginning, only about six hours, it is advisable to give capsules three times daily during the hay fever season. Quite a few patients suffer from their symptoms particularly during the early morning hours, because the pollination of many plants occurs at that time. In these cases, a fourth dose at 3 A.M. is helpful.

Patients taking oral therapy for the second season require smaller doses than they did for the initial course of treatment.

Here, as when parenteral therapy is employed, additional allergens such as dust, molds, rusts, and foods must be considered, and if necessary combated.

Contraindications to oral pollen therapy are existing gastro-intestinal disturbances, chronic diarrhea, colitis, gastric or duodenal ulcer, and chronic appendicitis.

TABLE 49—*Dosage Schedule for Preseasonal Oral Treatment with Grass Pollen Propeptan for Adults*

Date*	Dosage	Total Daily Dose (pollen propeptan units)
April 1-30	1 capsule a day	60,000
May 1-14	1 capsule twice a day	120,000
May 15-31	1 capsule three times a day	180,000
June 1-end of season	2 capsules three times a day	360,000

Each capsule contains 60,000 units of pollen propeptan. One unit of pollen propeptan is one microgram of specific pollen digest.

* Dates given are suitable for grass pollen hay fever throughout the northeastern section of the United States, but must be appropriately modified where the season differs significantly.

TABLE 50—*Dosage Schedule for Coseasonal Oral Therapy with Weed Pollen Propeptan for Adults*

Day No.	Dosage	Total Daily Dose (pollen propeptan units)
1	$\frac{1}{2}$ capsule	50,000
2	$\frac{1}{2}$ capsule twice a day	100,000
3	$\frac{1}{2}$ capsule three times a day	150,000
4	1 capsule three times a day	300,000
5	2 capsules three times a day	600,000
6 to end of season	2 to 3 capsules three times a day, depending on symptoms	600,000-900,000

Each capsule contains 100,000 units of pollen propeptan. One unit of pollen propeptan is one microgram of specific pollen digest.

TABLE 51—*Dosage Schedule for Coseasonal Oral Therapy with Grass or Tree Pollen Propeptan for Adults*

Day No.	Dosage	Total Daily Dose (pollen propeptan units)
1	$\frac{1}{2}$ capsule	30,000
2	$\frac{1}{2}$ capsule twice a day	60,000
3	$\frac{1}{2}$ capsule three times a day	90,000
4	1 capsule three times a day	180,000
5	2 capsules three times a day	360,000
6 to end of season	2 capsules four times a day	480,000

Each capsule contains 60,000 units of pollen propeptan. One unit of pollen propeptan is one microgram of specific pollen digest.

Coseasonal Oral Treatment.—Here a rapid increase in tolerance is desired. If no gastro-intestinal sensitivity is encountered, the schedule in Tables 50 and 51 may be tried, with the

understanding that if a reaction occurs after any dose, the next one should be reduced or the interval between doses lengthened

Since at this time the patient is absorbing variable amounts of pollen by inhalation, the first oral doses are relatively small

It might be well to stress once again that the physician must make every effort to adapt the dosage to the requirements of the individual case

Perennial Oral Treatment—The writers have observed many excellent results achieved with oral pollen propeptan therapy administered perennially

At any time after the season is over or at the conclusion of the preseasonal or coseasonal oral treatment, the patient continues to take 1 capsule a day of that propeptan mixture to the pollens of which he was found allergic. If he has two or three hay fever seasons he has to take 2 or 3 different kinds of pollen propeptans. The perennial maintenance dose for tree and grass pollen cases is 60,000 units, and for fall hay fever sufferers 100,000 units once daily on an empty stomach. This dosage is continued until two weeks before the onset of the season, at which time the schedule for preseasonal treatment is followed.

The dosage for children for perennial therapy must be proportionately smaller. For children from 8 to 12 years of age, the capsules should contain 60,000 pollen propeptan units of the weed pollens and 30,000 pollen propeptan units of the tree and grass pollens for those from 4 to 8 years of age, 30,000 and 15,000 units respectively. It will sometimes be necessary to remove the contents of the capsule and give them with water. When this is done, care should be taken to prevent the patient from inhaling any of the powder. For the preseasonal treatment a schedule somewhat like that in Tables 48 and 49 (according to the pollen season) should be followed, but of course with the capsule strength just given. The dosage may be similarly increased, provided that no untoward effects are noted. Coseasonal therapy should begin with 25,000 pollen propeptan units a day for weeds, and 15,000 units for grasses or trees, and thereafter be increased to a dosage one third to one half of that in Tables 50 and 51.

Reactions are discussed here chiefly as concerns oral therapy with whole pollen, since the

administration of pollen propeptans only occasionally is followed by side effects. There are three principal kinds of reactions: gastro-intestinal, which are seen rather often and focal and systemic, both of which are quite uncommon. The first type includes nausea, vomiting, severe cramps, colic, diarrhea, and, very rarely, appendicitis like pains; any of these may sometimes be so distressing as to interdict further oral therapy. Focal symptoms take the form of mild hay fever symptoms and very occasionally, of asthma. Systemic responses may give rise to dermatitis, urticaria, pruritus, malaise, headaches, and a feeling of exhaustion. Severe constitutional reactions of anaphylactic nature have not been reported. On the whole, the objective and subjective manifestations of hypersensitivity from therapy are less marked and distressing than those after hypodermic injections. Ephedrine sulfate, 0.048 Gm ($\frac{1}{2}$ grain) by mouth, usually suffices to combat these symptoms. Moreover, they can often be prevented—once they have made their appearance—by reducing the dose or by lengthening the intervals between doses.

Results of Oral Methods—It is impossible to give a fair account of the average results of oral pollen administration because many different preparations have been used (whole pollen, pollen propeptans, seed digest, liquid extracts), some in very small some in large doses. The majority of the authors mentioned on page 553 are of the opinion that the oral method, although still in the experimental stage, has a very promising future. The present writers favor it because they believe that when used as outlined above it achieves desensitization that ultimately leads to loss of specific hypersensitivity and thus to cure.

Finally, a method should be mentioned that was advocated by Schonwald²⁰⁸: the sublingual administration of the same extracts as those employed for hypodermic injection, although they need not necessarily be sterile. This procedure avoids the action on the pollen extract of the digestive juices and enzymes, and of the intestinal bacteria and fungi, as well as eliminating the irregularities of intestinal absorption. The concentration used is

about ten times stronger than the one tolerated by the patient subcutaneously, and such that not more than 4 or 5 drops are required for a single dose. Initially, 1 drop is taken in the morning and at bedtime, the quantity and frequency (up to three or four times a day) being increased until a beneficial effect is established. Gastro-intestinal reactions are not noted, but itching or swelling of the tongue or throat, or a spell of sneezing are indications that the amount should be decreased. As the hay fever improves or disappears the interval between treatments is lengthened until a maintenance dose is given, several days apart, for the remainder of the season. Schonwald prefers the preseasonal method for the sublingual route.

d) SYMPTOMATIC THERAPY

When previously untreated patients visit the physician for the first time, symptomatic measures are indicated until such time as the specific therapy begins to be effective. Similar methods will also be useful in cases in which specific treatment has, for some reason or other, failed. Symptomatic therapy may be either local or general. Numerous methods and medicaments have been recommended for the control of local hay fever manifestations, especially of the nasal symptoms. At best, the symptoms are alleviated by such treatment; occasionally, however, they are exacerbated. Nasal congestion or sneezing can be combated by instilling vasoconstrictors, such as ephedrine solution (2 per cent), neosynephrin hydrochloride (1 per cent), propadrine hydrochloride (3 per cent), privity hydrochloride (0.05 or 0.1 per cent), or tuamine sulfate (2 per cent). In very severe cases in which these agents are found to be irritating, cocaine (0.5 to 1 per cent) should be added, provided the patient is known not to be hypersensitive to it, and with due precautions regarding habituation. The following prescription is particularly effective:

	Gm. or Cc.	
R Cocaine hydrochloride	0.12	gr. ii
Ephedrine hydrochloride 1:1,000	0.2	gr. iii
Chloretone	0.12	gr. ii
Isotonic solution of sodium chloride	q. s. ad 30.0	f 3 i

M. Sig : Nose drops 3 times a day as necessary.

Instillation of these vasoconstrictors with a dropper is preferable to spraying, since the latter often causes mechanical irritation. Oily solutions or jellies containing the drugs mentioned are less irritating; but since they are absorbed less readily, they are also less effective. Liquid petrolatum with or without small amounts of camphor or menthol will usually alleviate the annoying sensation of "dryness" of the nasal membranes sometimes complained of by successfully treated patients.

For the relief of distressing ophthalmic symptoms, Estivin may be used, in severe cases, $\frac{1}{4}$ per cent neosynephrin hydrochloride or the following prescription is recommended:

	Gm. or Cc.	
R Holocaine	0.1	gr. iss
Ephedrine 1:1,000	4.0	f 5 i
Boric acid (saturated solution)		
Rose water	aa q. s. ad 30.0	f 3 i

Frequent bathing of the eyes with a cold 3 per cent boric acid solution in an eye cup is also helpful.

When systemic symptoms appear, it is advisable to administer ephedrine sulfate in combination with phenobarbital, seconal, or amytal two or three times daily:

	Gm.	
R Ephedrine sulfate	0.025-0.045	gr. $\frac{1}{4}$ - $\frac{1}{2}$
Phenobarbital	0.015	gr. $\frac{1}{4}$
Sig	t capsule every four hours until relieved	

	Gm.	
R Ephedrine sulfate	0.025-0.045	gr. $\frac{1}{4}$ - $\frac{1}{2}$
Amytal	0.045	gr. $\frac{1}{4}$
Sig	t capsule every four hours until relieved	

Many pharmaceutical houses have similar combinations available for this purpose. Since orally administered ephedrine is effective for only a few hours, the patient may be given an enteric coated preparation, such as Ensels ephedrine and seconal sodium (Lilly) or Luasmin (Brewer), before going to bed. These act in about three and a half to five hours after administration, thus relieving the dread early morning symptoms. Other sympathomimetic drugs, such as propadrine hydrochloride 0.025 to 0.048 Gm. ($\frac{3}{8}$ to $\frac{3}{4}$ grain), racephedrine hydrochloride 0.025 Gm. ($\frac{1}{4}$ grain), or neosynephrin hydrochloride 0.01 Gm. ($\frac{1}{8}$ Grain), may have fewer central nervous system side-effects.

When the picture is dominated by exudative symptoms calcium gluconate (10 cc intra-venously or 1 tablespoonful of granules three times a day by mouth) combats this symptom satisfactorily. If the patient simultaneously presents nervous tension calcibronat (Sandoz) in the same dosage is preferable. Profuse watery rhinorrhea can often be controlled by carefully adjusted doses of atropine.

The following methods among others have been recommended for general therapy: injections of histamine, peptone, tuberculin, vaccines of colon bacilli, bee venom, snake venom, oral histaminase.

Beckman⁸⁷⁴ who considers the cause of allergic reactivity to consist of a shift of the acid-base balance of the organism toward alkalosis advocates the use of nitrohydrochloric acid.

R Nitrohydrochloric acid (not dilute)	Cc	5 ivss
Distilled water	qs ad 120	13 iv

Sig. 1 teaspoonful in a glass of water after each meal and at bedtime.

Dilute hydrochloric acid (30 drops three times a day) in orange or lemon juice serves the same purpose. Furthermore Bishop has recommended a trial of the ketogenic diet.

Vitamin therapy should also be mentioned in this connection. Rappaport and his associates⁸⁸⁷ give 4 to 10 drops of viosterol daily (each drop containing 30,000 international units of vitamin D) about ten days before the onset of the hay fever manifestations. Hatha-way⁸⁸⁴ recommends doses of 4,000 units per kilogram of the patient's weight. Cohen warns against possible hypervitaminosis resulting from long continuation of this therapy. Vitamin C in large doses (250 to 500 mg daily) was suggested by Holmes and Alexander⁸⁸⁹ but their good results were emphatically not confirmed by Hebald⁸⁹¹, Engelsber,⁸⁹² Newbold,⁸⁹³ Friedlaender and Feinberg⁸⁹⁶ ourselves and others. Vitamin E is also of no value in the treatment of hay fever (Glaser and Dam⁸⁹⁵).

Lapp⁸⁹⁶ claimed excellent results with a

course of autogenous serum injections in a series of cases of hay fever and pollen asthma. The patient's own serum was administered subcutaneously in doses of 1 to 2 cc every other day. Many of the patients so treated remained free of colds for long periods of time.

The general methods should be resorted to only when for some good reason specific measures cannot be employed.

The host of local (nasal) measures employed ranging from simple caustic burning to surgical removal of turbinates and submucous resection of the septum will receive only brief mention here since according to the writer's own experience they are helpful for only a short time. The same is true for intranasal ionization with zinc sulfate which was extremely popular for a few years. This method consists in superficially cauterizing the nasal mucosa by iontophoretic application of zinc. Although it must be admitted that the method is of some value where nasal obstruction is predominant since it reduces excessive mucus secretion this approach cannot be recommended for general use because it produces an acute maxillary sinusitis in some cases, asthma in others and may even lead to atrophic rhinitis. Moreover zinc ionization is very painful and its effects last one season at best. Edmondson⁸⁹⁷ has recently advocated a special technique of intranasal cauterization by means of tampons soaked in anhydrous cupric and zinc sulfates along with an application of galvanocolloidal silver but this has not been shown to be free from the same criticisms.

Mention must also be made here of roentgen irradiation of the nose, intranasal application of ultraviolet rays by means of a cold quartz light and nasal diathermy; these methods have been abandoned by most authors as being of little avail.

Nasal filters are not entirely without danger. Since this method obliges the patient to breathe through his mouth there is the risk of bringing on bronchial allergization—i.e. asthma. On the other hand we cannot recommend too emphatically that patients who fail to show improvement for one reason or another equip their bedrooms with air cleaners operating on the electrostatic principle (Cnep and Green⁸⁹⁸).

⁸⁸⁴ HATHAWAY M L, REED C I, HATHAWAY M L and STRUCK H C. J. Allergy 5: 541, 1934.

⁸⁸⁸ HATHAWAY M L, REED C I and STRUCK H C. b.d. 8: 1, 1936.

⁸⁸⁹ GLASER J and DAM H. b.d. 15: 13, 1944.

⁸⁹⁶ LAPP A D. B. t. M. J. 1: 322, 1947.

⁸⁹⁷ EDMONDSON E E. Texas State J. Med. 39: 479, 1944.

⁸⁹⁸ CNEP L H and GREEN M A. J. Allergy 17: 193, 1952.

or preferably a regular air conditioner that can also control the temperature and humidity of the atmosphere at the same time.* Gardeners, laborers, and others who are obliged to work out of doors where they contact large quantities of pollen, and pollen-sensitive workers in flour, grain, and seed mills who are occupationally exposed, as well as those handling pollens in bulk, should wear a respirator, such as the no. 5 Bantam Light Weight Respirator† or the M.S.A. Dustfoe Respirator‡ Since these respirators do not offer protection to the eyes, such patients should wear dark goggles.

c) TREATMENT OF HAY FEVER DUE TO SCENTS OF BLOSSOMS

As mentioned on page 281, hay fever may occasionally be due entirely or in part to hypersensitivity to the odoriferous substances or volatile oils of plants. Deallergization of the patient by oral administration of minute doses of these oils has been successfully performed (Urbach³⁸⁶).

The essential oils of locust, jasmine, linden, and other blossoms cannot be recovered by the usual chemical methods. The senior author has therefore made use of the technic of enfleurage that is almost exclusively employed in the extraction of natural perfumes: wooden boards are covered thickly with lard and the blossoms—for example, of locust—are placed between them, and renewed from time to time for seventy-two hours. The lard takes on the taste and smell of locust, and can be shown by appropriate tests to contain the volatile allergen.

The material processed in this way was used by us for oral administration in a patient who was specifically hypersensitive to this tree and who suffered from severe attacks of hay fever symptoms during its blossoming period. The dosage employed was 2 Gm. four times daily, for two weeks. Thereafter, the patient, although living in a locust grove, became absolutely free of symptoms. She remained so during the ensuing year after again taking her "locust butter" for four weeks prior to the season.

The objection could be raised that during the manipulation required for the process of enfleurage, pollen

could come into contact with the fat, and so be responsible for the therapeutic success. To encounter this objection, the patient was tested nasally and found negative to locust pollen. A small amount of the fat containing the essential oil was introduced into her nose on an applicator as was also pure lard. While the latter had no effect, the former promptly elicited the symptoms of hay fever, this occurred only in the patient and not in control subjects similarly tested. Thus it was demonstrated that in this particular case the essential oil of the blossom and not the pollen was the allergen.

D. ALLERGIC LARYNGEAL EDEMA (ALLERGIC LARYNGOPATHY)

The clinical picture of laryngeal edema will receive some consideration in the section on angioneurotic edema (p. 759). The significance of heredity will also be mentioned there. According to Hansel,³⁸⁷ positive evidence of allergy could be found in some 65 per cent of cases with laryngeal edema. The cause cannot always be determined, as in a case reported by Waldbott.³⁸⁸ Edema of the glottis may occur in the course of urticaria, in allergic shock, and in serum sickness. Here we shall mention merely a few especially instructive cases.

Dollinger³⁸⁹ observed that he himself suffered from hoarseness after ingestion of milk and milk products, and that the condition could be made to disappear only by eliminating these foods from his diet. Objective manifestations included reddening of the laryngeal mucosa, with swollen mucous follicles extending to the larynx. The membranes were covered with a glassy and transparent mucus. Canestro reported a case of edema of the glottis following the use of a hair dye containing paraphenylenediamine, Trnmarchi, an instance in which the manifestations regularly appeared ten minutes after an injection of neoarsphenamine; Muench³⁹⁰ and Borries,³⁹¹ cases attributable to aspirin, and the latter author also a case due to novocain injections, and Worms and Gaud, a case in which the symptoms appeared following ingestion of herring.

When, as in the last-mentioned case, the laryngeal symptoms (painful spasms in the throat, severe attacks of coughing, distressing difficulty in swallowing) appear suddenly, one is naturally inclined to think, first of all, of some foreign body in the throat, and not of a

* It must be pointed out that hay fever patients do not tolerate cold air indoors; therefore the only air conditioners that are helpful are those that also permit regulation of the temperature.

† W. S. Wilson Corporation, 123 Varick Street, New York City.

‡ Mine Safety Appliances Co., Pittsburgh 8, Pa.

³⁸⁹ DOLLINGER, J. A. *Wien med. Wchnschr.* 86: 827, 1936.

swelling of allergic origin the correct diagnosis is usually not made until the physician observes that urticarial or other allergic manifestations develop simultaneously or subsequently. Examination of the hypopharynx reveals an edema of the mucous membranes.

As a rule, the patient can be relieved by means of ephedrine by mouth or in severe cases by a subcutaneous injection of epinephrine or by intralaryngeal adrenalin sprays, in some cases, however, tracheotomy must be resorted to (Fig. 262). Borries¹⁴ recommends that this be done without too much



FIG. 262 ANGIONEUROTIC EDEMA OF ENTIRE FACE AND OF LARYNX

Due to hypersensitiveness to neoarsphenamine and necessitating tracheotomy

delay since the allergic reaction can bring on such severe edema that even an operation is sometimes of no avail.

Cases in which the drinking of cold water brings on swelling of the mucous membranes of the mouth, larynx, and trachea (Duke¹⁵⁶⁷) are regarded as being of pathergic rather than of allergic origin (see discussion of cold urticaria, p. 411).

Certain characteristics paralleling those of angioneurotic edema are also shown by the so-called acute hypoglottic laryngitis. This disease picture which was described in detail

by Zimmerman as well as by Blumenthal¹⁰⁹⁰ is most commonly observed in children with the exudative diathesis according to Kuemmel who believes the condition to be attributable to an underlying allergy.

Spasm of the epiglottis may also be attributable to an allergic response, as in 2 cases mentioned by Waldbott²⁰³¹ who manifested severe spasm presumably due to an intravenous anesthetic administered prior to bronchoscopy.

Needless to say it is always necessary to establish the allergic origin of a given case before initiating any anti-allergic therapy and, aside from all manner of other causes the possible rôle of psychosomatic factors must always be borne in mind. The following case will serve as an excellent example.

A 37 year old intelligent teacher was referred with the problem of determining whether her occasional sudden spells of hoarseness were attributable to some allergy. In the course of her detailed personal history the patient who was giving instruction at various schools reported that on her way to a certain school she always passed a river and that she then regularly felt some strange pressure in her larynx following which her hoarseness would appear. She also stated that she had regularly observed similar symptoms after spending a short time in her damp cellar. One of us was able to confirm this by accompanying the patient to the cellar whereupon the possibility of molds playing the allergic rôle was naturally considered. Appropriate inhalation tests with fungi were performed and the results at first seemed to confirm the patient's statements. However the physician who referred her had pointed out that the adductor paralysis appearing during the spells of hoarseness strongly suggested a functional disturbance we therefore decided to have the patient treated first from the psychogenic angle. From the moment we gave the patient a certificate to the effect that her duties in a given school were physically injurious to her—and the school authorities promptly agreed to consider this recommendation—we were unable despite repeated attempts in the clinic to evoke any of the responses that previously had been regularly elicitable.

E ALLERGIC COUGH

Paroxysmal cough represents another allergic disease of the respiratory tract. This is characterized by a loud barking cough often of great intensity and force relatively non-productive, and lasting from a few minutes to hours or days. The patient has no systemic

¹⁰⁹⁰ BLUMENTHAL in *Handb. d. Hals, Nasen u. Ohrenh.* vol. 2, pt. 2, 1926.

symptoms, but complains of an itchy, scratchy, or grating sensation deep in the throat, leading reflexly to uncontrollable coughing spells. Periods of hoarseness also occur. The mechanism, according to Prigal,²⁰⁹¹ is an allergic edema of the mucous membrane deep in the throat, possibly involving the larynx. Kahn²⁰⁹² considered a case of chronic unproductive cough to represent an "allergic tracheitis." Differentiation from asthma is easy, since the patient has no dyspnea or other respiratory distress, and the chest is normal on physical examination. Roentgenologic study of the chest and examination of the sputum are negative.

Prigal lists as the evidence that this condition is allergic the marked familial and personal history of allergy, the positive skin reactions, although these tend to be slight, the therapeutic response to epinephrine and related drugs, the periodic nature of the illness, particularly with relation to contact with or avoidance of the causative allergens, and the response to hyposensitization.

Colmes and Rackemann²⁰⁹³ were able to demonstrate the allergic etiology of 3 cases by means of the histories, skin tests, and the fact that elimination of the allergen from the patient's environment was followed by freedom from this symptom. They found that face powder, feathers, pollen, and animal emanations were the principal causes of isolated attacks of coughing recurring over long

periods of time. Seasonal cases are usually due to pollens. Prigal²⁰⁹¹ found perennial cases to be caused by house dust, feathers and other animal danders, orris root, tobacco, and pyrethrum. It is possible that some instances of so-called tobacco or "smoker's cough" may be explicable as a hypersensitiveness to tobacco smoke. Foods play only a minor rôle in the production of this type of cough. Moreover, an allergic cough is very frequently observed as one of the manifestations of a generalized allergic response, especially in asthma and allergic rhinopathy. With regard to therapy, the principal measures are avoidance of the allergen when identified, or specific hyposensitization.

The complaint of cough in patients with allergic respiratory diseases is not at all rare in our experience and is chiefly caused by post-nasal drip, which in turn is generally due to a sinusitis. The latter is often bacterial in nature, sometimes allergic. Successful treatment of the cough depends on control of the sinusitis. This type of allergic cough is characterized by being more severe during the night—that is, in the recumbent position—and is sometimes present only at that time. During the day the patients swallow the nasal secretions, but at night they stagnate in the larynx and adjacent portions of the upper respiratory tract and stimulate the cough reflex.

Closely related to allergic cough, and indeed not always susceptible of differentiation, since allergic states may involve any or all parts of the respiratory tract, is allergic bronchitis, which is discussed in the next chapter.

²⁰⁹¹ PRIGAL, S. J. *Dis. Chest* 5: 115, 1942

²⁰⁹² KAHN, I. S. *ibid.* 3: 23, 1937

²⁰⁹³ COLMES, A., and RACKEMANN, F. *MI J. A. M.* 95: 192, 1930

ALLERGIC DISEASES OF THE LOWER RESPIRATORY TRACT

A BRONCHIAL ASTHMA

OF ALL the diseases due to hypersensitivity, the most important is bronchial asthma. This is true not only because it has the most frequent and incapacitating recurrences, making it a serious social and financial problem, but also because, when the accompanying diseases and sequelae are considered, mortality in asthma is by no means so small as is generally believed.

1 HISTORICAL INTRODUCTION TO THE THEORIES OF ASTHMA

The disease picture of asthma was already well known to the physicians and writers of ancient Greece and Rome (Hippocrates, Galen, Herodotus, and Aretaeus). The name is derived from the Greek word *ἀσθμα*, meaning "panting or gasping for breath." Celsus termed a slight degree of difficulty in breathing "dyspnoea", a more marked degree, "asthma", and the most extreme degree, "orthopnoea." While all of these authors gave descriptions—sometimes very detailed—of this condition, their explanations of its pathogenesis were purely philosophic and speculative. The doctrines of the Greek physicians dominated the field of medicine throughout the Middle Ages. It was not until the sixteenth century that Helmont emphasized the rôle of the nervous factor, and compared asthma with epilepsy.

In the following century three English physicians, who themselves suffered from asthma, became deeply interested in the disease. Thomas Willis was instrumental in bringing about general recognition of the importance of neurogenic factors in its etiology. He assumed that stimulation of the nerves surrounding the bronchi could cause an almost total bronchial occlusion. He also assumed that in addition to this "asthma convulsivum" there was such a thing as "asthma pneumonicum," resulting from obstruction of the bronchi. Floyer and Bree expressed the same opinions.

The eighteenth and nineteenth centuries

brought the establishment of a number of subdivisions of asthma, based on the symptoms or on the presumptive etiology. The most important of these and their outstanding champions were, in chronologic order: primarily neurotic etiology (Laennec), diathetic neurosis, interchangeable with dermatitis, gout, and migraine (Trousseau), bronchial spasm due to stimulation of the vagus (Longuet, Volkmann), sudden turgescence of the bronchial mucosa in order to expel irritating material (Bree, Weber), congestion of the lung (Bretonneau), spasm of the diaphragm (Wintrich), result of mechanical irritants in the bronchi, such as Charcot-Leyden crystals (Leyden) or Curschmann's spirals (Curschmann), result of a reflex mechanism originating particularly in the nose (Bruegelmann). As early as 1860, Salter noted the association of asthma with animal emanations, and also emphasized the importance of the hereditary factor.

Considerable progress was made in the twentieth century, when Meltzer²⁰⁰⁴ first called attention to the similarity between the bronchospasm seen in guinea pigs dying from anaphylactic shock (as first demonstrated by Auer and Lewis²⁰⁰⁵) and the bronchospasm in human beings during an asthmatic attack. On the basis of this observation, he regarded asthma as an allergic phenomenon. In the following years, numerous authors succeeded in experimentally eliciting or producing asthma in human beings and in animals, and also in effecting passive transfer of this state of hypersensitivity. While the experiments performed by these investigators demonstrated that a not inconsiderable percentage of cases are unquestionably attributable to an exogenous allergen, many others stressed the fact that it would certainly be erroneous to assume that the majority of them can be so explained. Furthermore, more recent investigations, to be discussed below, show that endogenous allergens—both auto endogenous

²⁰⁰⁴ MELTZER S. J. J. A. M. A. 55: 1071, 1910.

²⁰⁰⁵ AUER, J., and LEWIS P. A. J. Exper. Med. 12: 151, 1910.

and, above all, hetero-endogenous allergens, such as bacteria—play an important part in the causation and maintenance of asthma. Lastly, it was demonstrated that, in a very great proportion of cases, there is indeed an existing hypersensitiveness of the bronchial mucosa or musculature, but that it is non-specific in character, in other words, that these structures react to such varied stimuli as cold, wind, dust, excitement, and fatigue. In instances of this kind, the existing state of hypersensitiveness is to be regarded, according to our nomenclature, not as an allergy, but as a pathergy—the latter being frequently superimposed secondarily on the former

2. CLASSIFICATION

The differentiation of the types of asthma* continues to present very great difficulties. The reason for this is that recurrent attacks of paroxysmal dyspnea do not constitute a single etiologic disease entity, but rather a symptom complex. From the pathogenetic viewpoint, particularly early in the course of the disease and in the exogenous-allergic cases, they merely represent a reaction that, as Friedjung²⁹⁹ pointed out, should be considered as an exaggerated defense reaction. Thus, even the most severe asthma will disappear in a few hours, possibly forever, if the causative agent is discovered and removed.

The establishment of subgroups has been undertaken by various authors according to different points of view. M. Walzer,³⁰⁰⁷ Tuft,¹¹² and other prominent allergists subdivide the condition into two groups: (a) allergic bronchial asthma, "to include all those instances in which the asthma is the result of a specific allergic reaction, and to indicate that the attack is produced by sensitivity to a definite allergen"; and (b) non-specific bronchial asthma, "to include all other instances of asthma due to other intrapulmonary factors and not due to sensitization to specific allergens—as, for example, the asthma accompanying bronchitis (so-called asthmoid bronchitis), etc."

Ramirez²⁹⁹³ objects to this classification on the ground that, in the present state of our knowledge of allergy, the great number of cases placed under the nonallergic heading are often so considered simply because the demonstration of an allergic pathogenesis is not possible, this does not necessarily mean, however, that the symptoms are not due to an allergen, but merely that the allergen has not been found.

Furthermore, such a subdivision ignores the important fact that many cases do indeed present a hypersensitiveness of the bronchial mucosa, but that it is not specific-allergic but pathergic, or at least has become pathergic in the course of time.

Unger²⁹⁹ classifies asthma, on simple clinical grounds, into the paroxysmal and the chronic.

Walker in 1918 introduced etiologic classification of asthma on the basis of the results of skin tests with protein extracts. Cases in which positive reactions could be obtained were considered to be due to causes entering the body from without and were therefore called extrinsic, while those in which the causes were thought to be within the body were attributed to bacterial sensitivity and were called intrinsic. Cohen²⁹⁹⁹ added a third group in which, due to organic or functional complications, both factors play a part, the combined extrinsic and intrinsic group.

Rackemann²⁹ also classifies asthma cases on an etiologic basis, as follows: (1) extrinsic; (2) intrinsic, and (3) unclassified. The first group comprises all patients who are definitely hypersensitive to known specific substances. The intrinsic types are represented by those skin-negative individuals in whom no extrinsic cause is demonstrable. The intrinsic group thus includes such heterogenous conditions as reflex asthma, bacterial asthma, cardiac dyspnea, etc.

Walzer¹⁰⁰ suggests the subdivisions of atopic (hereditary) and nonatopic (nonhereditary) asthma. The difficulties inherent in this concept are fully discussed in the section on atopy.

A more detailed subdivision along the same

* Unless otherwise modified, the term asthma will here be used to mean bronchial asthma.

²⁹⁹ FRIEDJUNG, J. K.: *Ergebn. d. inn. Med. u. Kinderh.* 52: 16, 1931.

³⁰⁰⁷ WALZER, M.: *Bronchial Asthma*. In Tice, F. *Practice of Medicine*, Hagerstown, Md. Prior, 1924, sec. 3, vol. 3, p. 501.

²⁹⁹³ RAMIREZ, M. A.: *Arch. Otolaryng.* 28: 199, 1938.

²⁹⁹⁹ COHEN, M. B.: *Ann. Int. Med.* 29: 590, 1944.

¹¹⁰⁰ WALZER, M., COCA, A. F., and THOMSON, A. A.: *Asthma and Hay Fever in Theory and Practice*. Springfield, Ill. Thomas, 1931.

lines has been suggested²¹⁰² (1) atopic, (2) infectious, (3) mixed atopic and infectious, with definite evidences of both, and (4) non allergic or noninfectious, further subdivided into asthma due to physical allergy, bronchial stenosis, psychosomatic references, acute left ventricular failure (cardiac asthma), emphysema with wheezing, so called "intrinsic asthma," and that due to the nasobronchial reflex from nasal foreign bodies and polyps

Beresford²¹⁰³ has evolved a system for referring to the severity of asthmatic symptoms first degree or mild asthma, with essentially no interference with normal activity, and readily controlled by simple therapeutic measures, second degree or moderately severe asthma, with definite interference with normal activities and requiring large doses of therapeutic agents, third degree or severe asthma, with pronounced interference with normal activities, and controlled only by injection therapy, and fourth degree or very severe asthma, including status asthmaticus, not adequately controlled by any symptomatic therapy. Along with this, he advocates a notation of the seasonal or perennial and the continuous or intermittent nature of the symptoms. Thus, sample diagnoses might be "third degree asthma, perennial, intermittent 2 weeks," indicating recurrences about every two weeks throughout the year, or "fourth degree asthma, seasonal, fall, continuous"

The present writers are in agreement with all authorities on the point that the classification of the manifestations of this condition into various types is more or less arbitrary, and particularly that the patient may pass from one type to another with advancing age and according to the course of the disease. However, we have found the following scheme helpful in establishing a nomenclature based on pathogenesis

(1) *Allergic asthma*

- a) exogenous allergic asthma
- b) infectious allergic asthma
- c) tuberculo allergic asthma
- d) endogenous allergic asthma

(2) *Asthma due to bronchial irritation*

(3) *Psychogenic asthma*

(4) *Pathergic asthma, on the basis of (or induced by previous)—*

- a) exogenous allergic asthma
- b) infectious allergic asthma
- c) tuberculo allergic asthma
- d) endogenous allergic asthma
- e) psychogenic asthma
- f) irritation asthma

(5) *Asthma of unknown cause*

As is seen above, bronchial asthma can be divided, according to pathogenesis, into five main groups

The first group comprises the allergic types. Exogenous allergic asthma includes the cases due to a wide variety of inhalants and ingestants, and rarely to contactants and injectants. Naturally, pollen asthma belongs in this category. Infectious asthma represents the form initiated by infectious processes, which may be of three types—first and foremost, bronchitis, usually of chronic or recurrent nature, second, acute bacterial and virus diseases—particularly pneumonia, grippe, and whooping cough—and, much less frequently, focal infections. Tuberculo allergic asthma is a condition that develops on a tuberculous basis and is characterized by a high degree of hypersensitivity to tuberculin and by the appearance of asthmatic attacks in response to administration of a rather small dose of old tuberculin, for instance 0.1 cc of a 1:100,000 dilution (Urbach and Loew²¹⁰⁴). The term endogenous allergic asthma applies to the cases caused by allergens formed within the organism as a result of endocrine dysfunctions, intestinal disorders and other diseases that so alter the tissue protein as to render it foreign to the body. Altogether the allergic group was found to include 39 per cent of a series of 452 asthmatic ward patients whom the senior author²¹⁰⁵ classified according to the scheme above

Of the nonallergic asthmas, one type is caused by local irritation of the bronchial mucosa by a particular vapor or gas, chiefly in certain industries. Patients in this category, however, will rather quickly experience a broadening of the irritability of the bronchial neuromuscular apparatus, leading to a pathergic asthma (on the basis of irritation asthma)

²¹⁰² Edouard J. Allergy 16:199, 1945

²¹⁰³ BERESFORD, A. B. Correspondence J. Allergy 16:200, 1945

²¹⁰⁴ URBACH, E., and LOEW, A. Am. Rev. Tuberc. 42:174, 1940

The next group comprises cases of psychogenic asthma. Although one must never be too hasty in making such a diagnosis, the senior author³³ was obliged to reach the conclusion that psychosomatic influences were solely responsible for 3 per cent of his material. In this connection it must be stressed that emotional factors play some sort of a rôle in almost every case, yet it is only when the psychic conflict represents the principal cause of the condition that this diagnosis is warranted.

The majority of cases (58 per cent) fell into the pathergic group. This term denotes those hypersensitivities that are brought about by a variety of nonspecific agents, such as wind, cold air, changes of temperature, dusty atmosphere, offensive odors, fumes, and even emotional upsets. Pathergic asthma is here divided into six subtypes. One-half of all these cases originally had a bronchitis, and every exacerbation of this, usually as a result of a "cold," brought on asthmatic attacks. Subsequently such attacks were elicited by a great number of irritating factors. The remainder of the infectious cases, following pneumonia, grippé, whooping cough, measles, or focal infections, accounted for about one-fifth of the pathergic asthmas. Rather frequently (13 per cent)—and more commonly in women than in men—the primary condition was a psychogenic asthma, i.e., the dyspnea was associated with emotional conflicts, fright, deaths, operations, and similar experiences. Fairly often an allergic asthma became non-specific in the course of time. This was particularly rare, however, in the case of pollen asthma, and of the tuberculo-allergic and endogenous-allergic groups. As mentioned above, irritation asthma will nearly always lead in a relatively short time to a broadening of the hypersensitiveness of the bronchi.

Finally, there is a certain percentage of cases in which it is impossible to establish the nature of the pathogenetic mechanism. This is partly due to the inadequacy of our present methods of investigation, and partly to hidden factors that can be found only by chance. A third possibility resides in the clinical difficulties of discovering and proving the action of haptens and endogenous allergens.

3. INCIDENCE

On page 79 we endeavored to present the statistical evidence, gathered from various sources, concerning the frequency of bronchial asthma. Reports from hospitals are of relatively little value here, since asthma patients are rather infrequently hospitalized. The various estimates of incidence in the general population lie somewhere between 0.5 and 2 per cent, depending on the material of the author involved. Nor do we possess any very precise information concerning the distribution of the disease according to age and sex.

AGE

The majority of authors (Bray, Rackemann, Tuft, Vaughan, and M. Walzer) are of the opinion that from 30 to 40 per cent of all asthma cases begin in the first decade of life. About 50 per cent of all patients experience their initial attacks between the second and fourth decades, only some 12 to 18 per cent in the fifth and sixth decades; and a very small percentage after this age.

When the inheritance is bilateral, the symptoms first appear, according to Spain and Cooke,³⁶ during the first ten years of life in 79.1 per cent of cases, as compared with the figure of 36.3 for those without such inheritance.

In this connection, it is interesting to note that Friedjung³⁷ observed asthma in infants of from 3 to 6 weeks of age, and that Vaughan²¹ actually diagnosed typical symptoms in an infant not 3 hours old. On the other hand, the writers have seen, among 452 patients, 11 cases—8 men and 3 women—in which the initial attacks occurred between the ages of 61 and 70 years.

SEX

According to Bray²³ and the senior author³³ asthma is twice as common in boys as in girls. In the third, fourth, and fifth decades of life, there is a slight preponderance in favor of the female, amounting to about 7 per cent in our material; while in the age group over 50, men are more commonly afflicted than women. All in all, it would seem that men are somewhat more frequently affected than women, accounting for from 53 to 57 per cent of the total.

RACE

While it is the general impression that asthma is much more common in the white than in the Negro and in the yellow races and nearly unknown in the American Indian and the Eskimo all available evidence strongly suggests that this is due to mode of living rather than to racial influences (see p 81). This is confirmed by the medical experiences of the armed services in World War I (Davenport and Love¹⁰⁴) in normal males of military age more asthma appeared in Negroes than in whites and it was apparently more severe as regarded both morbidity and mortality. Derbes and Engelhardt^{2 65} were impressed with the large number of Negro patients seen at the Charity Hospital of New Orleans. Although the frequency was somewhat greater in whites the duration of the illness in each case was greater for the colored resulting in more time lost per individual. Similar findings were reported by Adams^{2 66}. Perhaps this discrepancy is to be explained by the observation of Smilie and Augustine^{2 67} that the vital capacity in the Negro race is markedly lower than that of the white. At any rate it must be concluded—and the experiences of the present authors confirm this—that asthma is a common disease among Negroes.

Gaillard²¹⁰⁸ found that the percentage of Jewish patients with asthma in his practice was about one third greater than that of the total population of the city.

OCCUPATION

There is no question that certain occupations are particularly prone to produce asthma. Workers so exposed include bakers, furriers, printers, cotton spinners, upholsterers, barbers and beauticians, hat makers, rag sorters, pharmacists, chemists, laboratory workers, dentists, woodworkers, poultry dealers, coffee, soy, cocoa, castor bean and other food handlers, jewelers, chromium workers

and refrigerator repairmen (Sternberg and Sorrell²⁹³). Derbes and Winsor^{2 69} have discussed the medico-legal aspects of occupational allergy of the respiratory tract.

SOCIAL STATUS

There is no variation in incidence as far as social strata are concerned. Rich and poor seem to be equally affected. However there is one appreciable difference in this respect as is well known: individuals who are under particular emotional strain (e.g. professional workers among men, housewives with many responsibilities among women) are the ones most likely to have asthma.

4 ETIOLOGY

As briefly mentioned above the etiology of asthma is by no means uniform. The confusion is increased by the fact that at least two components are required to bring on an attack: namely, the predisposing or contributory and the eliciting factors.

The fact that one looks only for the eliciting allergen and not for the factors that have rendered the organism allergic and maintain it in that state explains why the discovery of the allergen or pathergen in a given case—followed by appropriate therapy—often brings only temporary relief and not lasting cure. An instance reported by Black^{2 10} serves as an excellent illustration. A woman who had previously had asthmatic attacks only during a brief period in the spring and fall suffered severe seizures from the time she began working in a beauty shop. Whenorris root was eliminated and replaced by buckwheat flour the symptoms disappeared and remained absent for about ten months when they reappeared. At this time strongly positive skin reactions to orris root and buckwheat flour were observed while the skin test with rye flour was negative. After an interval of a year asthmatic symptoms again appeared and this time the cutaneous response to rye flour was also positive. In other words elimination of the exciting factor is of value for only a certain length of time for so long as the predisposing factor is not identified the organism continues to become hypersensi-

^{2 64} DAVENPORT, C. B. and LOVE, A. G. M. *Dept of U. S. Army*
in *World War* 13: 3-6, 1921.

^{2 65} DERBES, V. J. and ENGELHARDT, H. T. *Am J M Sc* 28:
675, 1913.

^{2 66} ADAMS, T. W. *Id* 184: 342, 1932.

^{2 67} SMILIE, E. W. G. and AUGUSTINE, D. B. *J A M A* 87: 20,
1926.

^{2 108} GAILLARD, G. E. *J A c y* 13: 611, 1942.

^{2 293} DERBES, V. J. and WINSOR, T. *Ann Int Med* 26: 25, 1944.

^{2 10} BLACK, J. H. *J A c y* 4: 24, 1932.

tive to more and more substances. We shall, therefore, first consider the circumstances and conditions that frequently constitute the fore-runners of allergy: i.e., those that are to be regarded as predisposing factors. It cannot be denied, of course, that it is often difficult to decide whether an existing infection or endocrine disturbance represents the predisposing disease or gives rise to substances that act as the precipitating agents (allergens or pathogens). The decision must depend, in a given case, on the history and on the results of exposure and elimination tests. It is always essential, however, to treat the predisposing factor—in so far as this is possible today—just as painstakingly as the agent immediately responsible.

a) FACTORS PREDISPOSING TO ASTHMA

(1) Heredity

Heredity is one of the most important constitutional predisposing factors in the etiology of asthma. This was first shown by Cooke and Vander Veer,²¹¹ and confirmed and elaborated by Spain and Cooke,²¹² who showed that there is not only a tendency for asthma to be inherited, but also that this tendency seems to be transmitted as a mendelian dominant characteristic. Many other authors, including Balyeat, Baagoe, Bray, Hanhart, Klewitz, Kaemmerer, Rackemann, Rowe, and Stiles and Johnston, have supplied data that served definitely to establish the importance of hereditary influences in the pathogenesis of asthma. While agreeing on the importance of heredity, Adkinson²¹³ is of the opinion that the transmitted character is a recessive one.

The significance of heredity is also supported by observations on identical twins. The literature contains reports on twenty-three pairs (Cooke and Vander Veer,²¹¹ Spaich and Ostertag,²¹⁴ Buffum and Feinberg,²¹⁵ Hanhart,²¹⁶ Crippe,²¹⁷ Urbach,²¹⁸ Ratner^{209, 219}).

In seven pairs, asthma appeared in one individual only; while in sixteen pairs both had the condition. The causes were said to be similar in eleven pairs, different in three, and were not mentioned in two.

On the other hand, it would be erroneous to postulate that a hereditary tendency is an absolute essential for the acquisition of this disease (see discussion of experimental asthma, p. 584).

(2) Autonomic Imbalance

Functional disorders of the autonomic nervous system are characterized by an imbalance with predominant parasympathetic tone (vagotonia) or predominant sympathetic tone (sympathicotonia), or by mixed hypertonia with components of both divisions (amphotonia).

It is now generally agreed that asthma very often represents a spasm of the circular bronchial musculature, which is innervated by the parasympathetics, and can be relieved by sympathomimetic drugs, particularly epinephrine. In view of this fact, and under the influence of the Eppinger-Hess school of thought, asthma was originally regarded as a vagotonic disturbance. Consequently, vagal irritation may ensue and, in turn, produce bronchial constriction. This viewpoint was also supported by the fact that parasympathomimetic drugs (e.g., mecholyl) invariably produce wheezing paroxysms in asthmatics, while control subjects manifest no chest symptoms, but only general signs of parasympathetic stimulation (Moll²²⁰). The nocturnal onset of the attacks was also explained by some as the result of the increased vagal tone during sleep, while the fact that the asthmatic attacks fail to appear during a disease associated with fever, has been attributed to the increased sympathetic tone during fever. It is known today that the division of imbalances of the vegetative nervous system into vagotonia and sympathicotonia is arbitrary; that, from the clinical point of view, mixtures of both types are more common; and that, indeed, both are involved in producing bronchospasm. It is therefore more appropriate to speak of an autonomic imbalance, or to use the broader term neuro-vegetative dystonia.

²¹¹ COOKE, R. A., and VANDER VEER, A., JR. *J. Immunol.* 1, 201, 1916.

²¹² SPAIN, W. C., and COOKE, R. A. *ibid.* 9, 571, 1924.

²¹³ ADKINSON, J.: *J. Genetics* 5, 363, 1923.

²¹⁴ SPAICH, D., and OSTERTAG, M. *Zschr. f. menschl. Vererb.-u. Konstitutionslehre* 19, 731, 1936.

²¹⁵ BUFFUM, W. P., and FEINBERG, B. *J. Allergy* 11: 694, 1940.

²¹⁶ HANHART, E.: *Klin. Wchnschr.* 16: 1407, 1937.

²¹⁷ CRIPPE, L. H.: *J. Allergy* 13, 391, 1942.

²¹⁸ URBACH, E.: *Wien. klin. Wchnschr.* 83: 761, 1935.

²¹⁹ Discussers to Ratner²⁰⁹.

²²⁰ MOLL, H. EL.: *Quart. J. Med.* 9: 229, 1940.

Thus Kappis showed that the centripetal portion of the reflex arc runs in the sympathetics and the centrifugal portion involves the vagus. Sato¹⁷ demonstrated that the spinal sympathetics innervate the bronchial constrictors by showing that section of the posterior roots in the upper thoracic region results in a definite dilatation of the bronchi while asthma like respiratory disturbances are produced when they are subjected to mechanical irritation.

While there seems to be little doubt that vasomotor instability is an important constitutional factor in the mechanism of asthma it can hardly be regarded as the sole cause for vagal stimulation will not cause asthmatic symptoms in healthy human beings. On the contrary a definite stimulus of allergic pathergic or psychoneurogenic nature is necessary to evoke an attack even in a vasolabile asthmatic. But fluctuations in the tone of the vegetative nervous system may perhaps explain why a patient will at times suffer an attack on contact with a given allergen but not after a similar exposure at other times.

Bronchospasm or paroxysms of bronchospastic dyspnea need not necessarily be based on nervous hyperirritability of the autonomic nervous system. The bronchial musculature tends very frequently to react directly and therefore low grade stimulation can elicit spasm. Moreover it can be demonstrated that hypersensitiveness of the bronchial mucosa can play an important part in the development of the disease in many cases.

(3) Psychosomatic Factors

More and more recognition is being accorded to the importance of psychosomatic influences in the development of asthma and most particularly in the precipitation of attacks in many cases especially of the pathergic group. Naturally the pathogenetic role of the psychic factor is even more difficult to demarcate than that of any of the others. Nevertheless there are a number of explanations that seem to coincide with practical medical experience and that therefore merit brief discussion here. The psychic component can exert its influence by increasing the irritabil-

ity of the organism. On the other hand attacks of asthma may occasionally be due to a lowering of the organism's threshold of irritation under psychogenic influences. Furthermore it is to be recalled that many cases in which the asthma is originally of allergic causation eventually undergo a loss of allergic specificity with the result that emotional upsets can also evoke attacks—probably through a conditioned reflex mechanism. In this connection it would be well to recall Metalnikov's experimental investigations¹⁸ of the conditioned reflexes in which he found that the sensory or acoustic impressions ordinarily accompanying an allergic reaction are capable of eliciting immunologic reactions without the intervention of the causal allergen (see p. 75). The majority of investigators of the behavioral significance of the psychic features in the asthma syndrome conclude that the symptoms represent manifestations of anxiety and nervous irritability or serve as protest evasion or escape. Others regard the symptoms as attention getting devices, results of suggestion, childish histrionics, imitations or simple conditioning.

On the basis of careful psychiatric evaluation Brown and Goitein¹²³ noted that the time relationship of the asthmatic attack to frustration and emotional tension is explained by displaced affects of rage, the guilt libido thereby finding equivalent gratification. Both French and Alexander⁴ and Oberndorf¹²⁴ have propounded the thesis that the attack is the equivalent of a suppressed cry, the patient having been frustrated in early life and forbidden to cry.

Further light is shed on the psychosomatic relationships in this disease by the fact that personality data of asthmatic patients point to a single fairly definite personality constellation. According to Rubin and Moses¹²⁵ these patients seem to comprise a fundamentally passive dependent group of individuals who were children of an overprotective dominating mother. They have not cared for, striven for or gained any marked degree of independence in life and continue to seek care

123 BROWN, E. A. and GOITEIN, L. J. *Nerv. & Ment. Dis.* 98: 638, 1943.

124 FRENCH, T. M. and ALEXANDER, F. *Psychosom. Med. Monographs* 11 and 15.

1 KAPF, S. M. *Med. Klin.* 20: 1347, 1924.

17 SATO, S. *Klin. Wchnschr.* 1: 1723, 1936.

and protection from the environment. The studies of Brown and Goitein²¹² indicate that asthmatic subjects are of a cyclothymic disposition associated with paranoid features, repressed hostility, and self-punishment motives. Rogerson²¹³ describes them as overactive, restless, excitable, alternately showing anxiety, timidity, fearfulness, and insecurity, or irrationality, aggression, and domineering behavior. In a study of forty asthmatic patients, Schatia²¹⁴ found evidence of psychoneurosis of the obsessive type, while Rorschach tests revealed a tendency to be rigid in reactions and to cover emotional turmoil by excessive intellectualization, with an attempt, whenever possible, to take refuge from a hostile environment by engaging in a fantasy life. The patient has an anxious, cautious, and unfree kind of affective adaptability, and especially an inclination toward a depressive trend which he tries to master in the presence of others.

Whatever the real explanation may be, practical experience has shown that psychosomatic mechanisms may never be ignored. Indeed, in many cases it is difficult, not to say downright impossible, to find any cause other than the psychic factor. In such instances, referred to as psychogenic asthma, the principal therapeutic approach is necessarily psychic treatment, which gives the best results. In a few especially severe cases, it is advisable to refer the patient to a psychotherapist. Interesting studies of the psychology of the asthmatic were written by French and Alexander²¹⁵, by Strauss,²¹⁶ and by Weiss and English,²¹⁷ among others. They point out that psychologic and allergic factors probably stand in a supplementary relation to each other. In many cases, at least, it is not a question of either an allergic or psychologic etiology, but of some sort of synergism between the two. Brown and Goitein²¹⁸ have contributed an interpretation of asthma from the psychoanalytic point of view, and reach the conclusion, among others, that "sensitIVITY" is displaced repressed sexuality. Stokes,

Kulchar, and Pillsbury²¹⁹ have drawn a significant parallel in the psychogenous field between asthma and urticaria.

Nowhere is the importance of psychosomatic references more clearly delineated than in the childhood asthmatic. Hence the parents should be instructed never to show the slightest sign of alarm should the child have an attack, and never to talk of the "wheezy noises" or let the child think there is anything unusual about his breathlessness. When an attack occurs, they are advised not to send for the doctor, if possible, or at least not to let the child know the doctor is coming, so that he may be spared from sharing in the anxious state of expectancy occasioned by waiting for the physician.

Although there is scarcely any doubt that psychic influences are of particular importance in the production of asthmatic attacks, the diagnosis of "primary psychic asthma" should be made only with the utmost care, and, indeed, should never be considered at all until the case has been subjected to thorough investigation from the allergic as well as from the psychiatric viewpoint.

Lastly, since there is a close interrelation between disturbances of the autonomic and the central nervous system, the frequent association of a psychoneurotic element with autonomic imbalance may be more readily understood.

(4) *Endocrine Disturbances*

Functional disturbances of the individual endocrine glands, especially the ovaries and thyroid, or of the endocrine balance, either in themselves, or via the circuitous route of the autonomic nervous system, can act as factors predisposing to asthma. Moreover, the same conditions may lead to the formation of autoendogenous allergens that can constitute the direct cause of asthma. Since we are not as yet in a position to differentiate between these two pathomechanisms, we are obliged to consider them together.

The asthma-inducing influence of menstruation is a well-known fact. The attacks most commonly appear during the menstrual period itself or—although rarely—in the post-

²¹² ROGERSON, C. H. *Quart J Med* 6, 367, 1937.

²¹³ SCHATIA, V. *Psychosom Med* 3, 137, 1941.

²¹⁴ FRENCH, T. M., ALEXANDER, F., et al. *Psychogenic Factors in Bronchial Asthma*. Washington, D. C. Nat. Res. Council, 1941.

²¹⁵ STRAUSS, E. B. *Guy's Hosp. Rep* 85, 213, 1937.

²¹⁶ STOKES, J. H., KULCHAR, G. V., and PILLSBURY, D. M. *Arch Dermat & Syph* 31, 470, 1915.

menstrual phase. A given patient will however usually have symptoms at the same point of the cycle. These cases are not to be confused with those in which asthma appears exclusively at the time of menstruation (Curschmann³⁰ Kaemmerer³⁰⁵ and many others including the authors). The present writers assume the presence of an endogenous allergy to the estrogenic hormone in the last mentioned type of case as well as in those in which the asthmatic attacks cease completely from one to three months after the beginning of pregnancy only to reappear when the patient begins to menstruate again (Shaw²³¹ Krohn and Urbach) and also in those instances in which the menopause terminates the asthma. This concept received confirmation from the observations of Zondek and Bromberg³³⁶ that such cases manifest skin reactivity to properly performed tests with synthetic estrogenic hormones. In cases with a definite correlation between menstruation and asthma Waldbott and Bailey² were able to demonstrate a deficiency of estrogen in the blood. This may possibly explain the good results obtained with hormone therapy in not a few cases of menstrual asthma. Alice¹³³ reported gratifying results with corpus luteum extract or with combined pituitary-ovarian preparations. Moreover Geber and the writers were able to produce lengthy remissions by intracutaneous injections of autogenous blood serum withdrawn at the height of the premenstrual asthma (see p 128). In especially severe intractable cases cure can be achieved through roentgen castration.

Jimenez Diaz¹³⁴ observed cases in which the asthma initially appeared at the beginning of pregnancy and disappeared toward its end. He explains this not on the basis of an ovarian hypofunction but in Zondek's sense on the basis of a hyperfollicular phase that brings about involution of the ova.

The menopause sometimes tends to alleviate the asthma but it not uncommonly exacerbates the condition in which case appropriate hormone therapy yields good results.

Furthermore one rather frequently encounters reports of the simultaneous appearance of asthma and hyperthyroidism. Thus Curschmann observed 2 patients who suffered from intermittent Graves' disease and invariably suffered genuine asthma attacks coincidentally with the more pronounced thyrotoxic symptoms. Curschmann advanced the hypothesis that the organism is sensitized to the abnormal secretion of the thyroid which acts as a foreign protein and which we would now term an endogenous allergen. Epstein²²⁹ reported four cases of asthma associated with hyperthyroidism and stated that it occurs more frequently in hyperthyroid than in hypothyroid states. Waldbott^{2,3} achieved cure of asthma by thyroidectomy of hyperplastic thyroids after other measures failed. Widal and Abram, Danielopolu, Wiehler and others reported improvement in the asthma condition after roentgen or radium irradiation of an enlarged thyroid gland. Waldbott²¹³⁵ and Maranon²³⁶ on the other hand observed a number of cases of asthma and of hypothyroidism that were cured by the administration of desiccated thyroid.

With regard to pancreatic function Abrahamson²³⁷ emphasizes the infrequency of association of asthma and diabetes and suggests a reciprocal relation between the two diseases. He assumes that hyperinsulinism is one of the conditions necessary for the appearance of asthmatic attacks and found that in asthmatic patients the glucose tolerance curves were typical for dysinsulinism—a characteristically diabetic curve for the first two hours followed by a precipitous drop as the test was prolonged. He relates the occurrence of nocturnal asthmatic attacks to a state of hypoglycemia. Goltman³⁸ on the other hand points out that asthma is associated with diabetes more frequently than is usually suspected and advocates that when competent allergic therapy fails to afford relief to the severe asthmatic diabetes should be ruled out since it may aggravate and prolong the disease.

³⁰ CURSCHMANN, H. Verhandl. d. deut. h. f. inn. Med. 38: 125, 1926.

²³¹ SHAW, R. E. J. A. M. A. 113: 186, 1939.

³⁰⁵ WALDBOTT, G. L. and BAILEY, L. J. J. Allergy 13: 125, 1944.

¹³³ ALICE, C. Bull. med. Pa. 549: 84, 1935.

¹³⁴ JIMENEZ DIAZ, C. El asma y otras enfermedades alérgicas. Madrid, 1932.

² WALDBOTT, G. L. Ann. Allergy 3: 12, 1944.

²³⁶ MARANON, N. G. First Internat. Cong. on Asthma, Mont. Do. 1932, p. 43.

²³⁷ ABRAHAMSON, E. M. J. Clin. Endoc. vol. 1, 402, 1941. U. S. Navy, M. Bull. July 1942, p. 711.

³⁸ GOLTMAN, A. M. Southern M. J. 35: 854, 1942.

(5) Acid-Base Balance

Metabolic studies in asthma seem to indicate that there is a temporary or permanent shift in the acid-base balance toward the alkaline side. Under normal conditions, the potassium-calcium ratio in the blood is constant (approximately 2:1); but, as Schittenhelm, Kylin, and others have demonstrated, the potassium content of the blood is markedly increased during an asthmatic attack, while the calcium content decreases at the same time. Furthermore, it is a well-known fact that seizures are more frequent at the time of physiologic alkalosis in the spring, and occur only rarely in patients with diseases accompanied by acidosis (e.g., fever or diabetes mellitus). While Wichmann and Paal, Klewitz and Schaeffer, Ellinger and Tiefensee consider alkalosis a prerequisite for asthma, Diehl and Schenk and Jimenez-Diaz and Franquelo regard alkalosis as the result and not the cause of the allergic state. Disturbances in the electrolytic balance were formerly attributed to increased vagal tone. Today, however, the reverse is considered more likely—namely, that there is increased activity of the parasympathetics as the result of the overbalancing of the calcium ions by the potassium ions, and on this basis the administration of calcium, intravenously whenever possible, was recommended for asthma. Tiefensee also favors an attempt to shift the asthmatic's metabolic balance from the alkalotic side back to the acid direction, by means of either diet or drugs (ammonium chloride).

(6) Infections

In the judgment of numerous authorities, and in the writers' own opinion based on clinical observations, infections are of dominant importance, both as predisposing and as directly eliciting factors. These include acute and chronic infectious diseases, particularly of the respiratory tract (bronchi, lungs), as well as bacterial infections of the nose and sinuses, and occasionally of the tonsils, teeth, and other organs.

The question as to whether the infectious agent has antigenic action in itself, or whether the inflammation of the tissues caused by the micro-organism paves the way for an allergic asthma, must be decided in each case on the

basis of the history, the clinical course, and the results of skin tests with bacterial vaccines and bacterial toxins, every attempt must be made to find the correct answer to this question, for it is of decisive importance in determining the pathogenesis, and thus in selecting the appropriate therapeutic approach. The relationship of infection to asthma may be divided into four categories:

1. *Bronchial Infections.*—The association between infections of the bronchial tree and asthma may be threefold. (1) A patient suffering from long-lasting or frequently recurring inflammation of the respiratory tract may absorb appreciable quantities of bacterial protein and thus become hypersensitive to bacterial products present in his bronchi or alveoli. In adults, one of the conditions most commonly leading to bronchitis is grippé. However, it is not the influenza virus itself that seems to be responsible for the broncho-pulmonary inflammation; it is rather the normally saprophytic bacteria of the upper respiratory tract that become pathogenic as a result of the marked reduction of immunity due to the grippé. In such cases, hypersensitiveness to the proteins (or polysaccharides) of these micro-organisms and not to their toxins may be assumed. Such cases usually exhibit well-defined differences from exogenous-allergic asthma (see Table 55, p. 623). (2) Moreover, in a rather large group, respiratory infections pave the way for sensitization by other allergens. Thus, a bacterial infection of the respiratory tract may injure the mucous membranes and thereby predispose them to allergization by exogenous allergens (animal emanations, dust, chemicals, and other inhalants). However, hypersensitiveness to bacteria may develop even in these cases, thereby establishing a vicious circle. (3) In still other instances, asthma of nonbacterial origin leads to secondary bronchial infection. This type of secondary chronic bronchitis is not to be confused with bacterial asthma caused by respiratory infection, as described above. Moreover, Turnbull²¹³⁹ has pointed out that failure of resolution of ordinary pneumonia may be due to existing respiratory allergy and will respond to appropriate treatment of the latter.

Finally, it should be borne in mind that the secondary bronchial infection particularly in elderly individuals, may overshadow the primary allergic hypersensitiveness.

2 Focal Infection—Aside from bacterial invasion of the bronchi infections in other organs occasionally play a part, both in allergizing the organism and in providing the eliciting allergens. Evidence of this possibility is provided by those cases in which tonsillectomy or dental extraction, or control of a sinusitis by surgical intervention or chemotherapy, leads to the disappearance of the asthma.

The controversial opinions as to the etiologic importance in asthma of pathologic conditions of the nose and its accessory sinuses, have been discussed in some detail in the sections on rhinopathy and sinusitis. In agreement with the majority of authors, the writers are of the opinion that when bronchial and nasal infections coexist, they are usually concomitant and due to the same microorganisms. There may be some occasional cases, however, in which a sinusitis acts as a focal infection that allergizes the bronchial mucosa. This results from the absorption of bacterial products into the lymph or blood vessels, permitting these products to act as antigens or toxins (thereby leading to a hypersensitiveness to bacterial protein or to bacterial toxins), and thus promoting asthmatic attacks. Furthermore, the constant drainage of pus from infected nasal tissues may mechanically irritate the bronchi, and so bring on asthmatic paroxysms. This occurs particularly during sleep. For a further discussion, the reader is referred to the section on asthma and rhinopathy below.

3 Toxin Hypersensitiveness—In some instances, bacterial infection may give rise to asthma from hypersensitiveness to bacterial toxins rather than to bacterial proteins. This may be assumed in those cases in which skin tests with toxin containing bacterial filtrates (not the usual vaccines) are negative. The situation is analogous to that in the Schick and Dick tests.

Whatever the exact pathogenetic relationship may be in a given case, the fact remains that in a high percentage of all cases, asthma appears as a sequel to acute infectious diseases of the respiratory tract, and it is also well known that pneumonia is very commonly en-

countered in the personal histories of asthma patients. Moreover in a previously allergic individual aggravation of allergic symptoms may follow a respiratory tract infection and under such circumstances chronic asthma not infrequently will recur after a lapse of years. Kaemmerer found that upper respiratory tract infections immediately preceded asthma in 56 per cent of his material, and pneumonia in 59 per cent. According to Gram, the initial asthmatic attacks appeared promptly after a grippé or a pulmonary infection in 69 per cent of his cases. Hajos was able to establish a direct connection between the first asthmatic attack and some catarrhal or inflammatory disease of the mucosa in 40 per cent of his cases. In a series of 607 asthmatics Evers found that pneumonia, pleuritis, grippé, or pertussis had immediately preceded the initial attack in 31 per cent of the cases, and that this figure rose to 80 per cent when common colds and bronchitis were similarly considered. Walker, Thomas, Peshkin, Rackemann, Schneider, and many others reported similar observations. The present writers' own material revealed histories of infectious diseases of the respiratory tract or coryza in a high percentage of asthma cases. In children too, bronchopneumonia, bronchitis, grippé, pertussis, and other infections, such as measles, play an important role in this respect. Tuscherer was able to demonstrate the presence of infectious allergy in 34 per cent of 650 cases.

Van Leeuwen¹¹⁰ rejects the view that bacterial infections are of special importance in the pathogenesis of asthma, on the grounds that there is no appreciable difference between so-called bronchitis asthma and exogenous-allergic asthma so far as the bacteriology of the sputum is concerned, and that skin tests with bacterial vaccines are not dependable. However, these reasons do not constitute convincing arguments. As for the question of skin tests with bacterial preparations, van Leeuwen himself points out the striking fact that he noticed absence of skin reaction in the bronchitis group, he thus raises the question whether decreased or even totally lacking reactivity to streptococcus

¹¹⁰ LEEUWEN W. S. VAN and LEEUWEN A. J. S. VAN Tischer. I. Immunitätsforsch. u. exper. Therap. 76: 109, 1932.

vaccine might not be considered analogous to the negative response in the Schuck test. Sterling and Walker go so far as to interpret failure to respond to the skin test as conclusive evidence of the bacterial origin of asthma. But this conclusion might in turn be disputed by pointing out that tests with the bacterial vaccines now in common use do not permit any definite conclusions, since the protein is largely denatured in the course of their preparation. In agreement with Cooke and Grove²¹¹ and other authors, the present writers are of the opinion that a positive skin reaction may be regarded as specific only when a focal reaction—i.e., an attack of asthma—is elicited at the same time.

Kaemmerer²¹² found that in the majority of asthma cases the sputum contains *Streptococcus viridans*. He regards these micro-organisms as normal saprophytes of the upper respiratory passages, but holds that they become transformed into antigens when, as a result of depressed immunity, they break through the natural barrier of the mucous membranes and are then absorbed. On the other hand, Valéry-Radot²¹³ believes that the significance of the pathologic micro-organisms in the bronchi of asthmatics lies in the fact that they determine the intensity of the bronchitic process, which in turn unfavorably influences the asthma. Correspondingly, he considers the value of vaccine therapy to consist entirely in the increased resistance to the bacteria maintaining the bronchitis.

4. *Tuberculosis*.—Lastly, the question remains to be considered as to whether tuberculous infections of the lungs are of significance in the production of asthma. The older clinicians, such as Rokitansky, as well as a number of recent investigators, such as Bandler and Roepke, Bruegelman, Schroeder, and others, are of the opinion that asthma and tuberculosis are mutually exclusive, or at least that the incidence of such infections among asthmatics is no greater than among individuals suffering from other diseases. Conversely, a study of nearly 400 cases with active pulmonary tuberculosis by Tocker and David-

son²¹⁴ showed the incidence of asthma to be approximately the same as in the general population. On the other hand, certain authors such as Mueller, Jiménez-Díaz, Turban and Spengler, and others stress the frequently observed combination of asthma and tuberculosis and point out that tuberculosis causes a lowered resistance of the lungs that, in turn, predisposes the organism to asthma (J. Bauer). As regards the emphasis placed by the latter group on the extreme hypersensitiveness to tuberculin manifested by many asthmatics, it must be said that this alone does not in any way warrant the conclusion that the asthma is of tuberculous origin, for these reactions may be expressions of a metaspecific allergy. This is well illustrated by the findings of Oatway, Gale, and Mowry²¹⁵ that patients with tuberculous tracheobronchitis who were most sensitive to tuberculin were also sensitive to routine allergen skin tests. For some reason, cases of tuberculous tracheobronchitis reacted more strongly to allergic tests than did tuberculous patients without such lesions, and the most serious bronchial lesions occurred in women with clinical evidence of allergy.

Consolidations in the apex, old scars in the hilar region, calcified primary complexes and hilar lymph nodes, all of which unquestionably indicate recovery from a tuberculous infection, in themselves emphatically do not speak for or against the likelihood of a tuberculous origin of the asthma.

Waldrott²¹⁶ points out that asthma may stand in any of four relationships to tuberculosis: (1) Asthmatic wheezing is encountered during the course of tuberculosis and is easily confused with asthma. Enlarged tuberculous glands, strictures of bronchi, and mucus and caseous material lodged in bronchi may induce bronchospasm in patients who are not allergic. A pertinent case reported by Herbut²¹⁷ showed at necropsy narrowing of the diameters of the terminal bronchi due to the presence of tuberculous granulomas throughout their walls. Active tuberculosis accounted for 4 per cent of Fraenkel's²¹⁸ "asthma"

²¹¹ COOKE, R. A., and GROVE, R. C. *Arch. Int. Med.* 56: 779, 1935.

²¹² KAEMMERER, H., and WEISSHAAR, M.: *Deutsches Arch. f. Klin. Med.* 131: 4, 1935.

²¹³ VALÉRY RADOT, P., BLANCHETIER, P., and NÉRET, F. *Presse méd.* 44: 449, 1936.

²¹⁴ TOCKER, A. M., and DAVIDSON, A. G. *J. Allergy* 13: 108, 1944.

²¹⁵ OATWAY, W. H., JR., GALE, J. W., and MOWRY, W. A. *J. Thorac. Surg.* 13: 1, 1944.

²¹⁶ HERBUT, P. A. *Arch. Path.* 39: 338, 1945.

²¹⁷ FRAENKEL, E. M. *Brit. M. J.* 1: 216, 1943.

cases (2) Allergic asthma may become complicated by tuberculosis although this appears to be rare. According to Tocker and Davidson²⁴⁴ asthma is often favorably influenced by active intercurrent pulmonary tuberculosis. However the asthma acts un favorably on the infectious process since the paroxysms of the former by reason of the intense cough and increased secretions facilitate bronchogenic spread of the tuberculosis from an active caseo pneumonic focus. This unfavorable effect is particularly marked in patients with therapeutic pneumothoraces because of the disturbances in intrapleural and intrapulmonary pressures sometimes causing temporary re expansion of the lung and even reopening of cavities (Vaccarezza and Cacchiani Avacedo²⁴⁵). (3) Tuberculosis may be followed by allergic asthma—or hay fever—and this is not uncommon. (4) In some asthmatic patients with healed tuberculosis there are strong skin reactions to tuberculin while the usual skin tests for allergy are not conclusive and complete relief may be afforded by tuberculin therapy in small doses.

Every asthma patient should be subjected to thorough physical and roentgenologic examination for tuberculosis; the sputum should also be investigated. In our own material²⁴³ it was possible to demonstrate a tuberculo-allergic pathogenesis in about 5.5 per cent of all asthma cases (for a further discussion see the section on tuberculo-allergic asthma p. 608).

Only a few French authors consider syphilis to play any particular part in the pathogenesis of bronchial asthma.

(7) Intoxications

Little is thus far known concerning the role of intoxications as factors predisposing to asthma. In the section on infections above, brief mention was made of the fact that many have considered the possibility that asthma might occasionally be attributable to toxicity rather than to the infection itself since bacteria can act not only as antigens in themselves but also by means of their toxins. Another possibility is that as the result of bacterial activity of a pathologic intestinal

flora or owing to resorption of abnormal degradation products of the intestinal contents parasympathetic nerves are stimulated (Hofbauer²⁴⁶). Other authors such as Kaemmerer³⁰⁵ explain the bronchospastic effect of intestinal toxins as due to the absorption of histamine like substances in certain predisposed individuals in whom there is inadequate detoxification on the part of the liver. In any event it is advisable to deal with any existing chronic digestive disturbance by prescribing an appropriate diet and not by means of laxatives.

(8) Mechanical and Chemical Irritations of the Mucosa

Injury to the bronchial mucosa by chronic mechanical or chemical irritation is a factor that is rarely accorded due consideration as a predisposing or contributory cause of asthma. It is readily demonstrable however that asthma may be an occupational disease particularly in the case of pursuits in which repeated irritation of the respiratory tract brings on chronic inflammation of the mucous membranes or in which inhalation of dust particles actually damages the mucosa. The following substances may be mentioned as commonly encountered respiratory irritants: bed feathers with their minute points, street dust containing fragments of stone as well as smoke, chalk dust, irritating chemical fumes, odors, dyestuffs and various drugs. Prophylactic measures consisting of proper ventilation and masks are often of great value.

While the factors mentioned above act from without it must be borne in mind that mucous plugs in the bronchial tree, purulent secretions in the bronchi and the contents of bronchiectatic dilatations also constitute important mechanical irritations. They probably represent the chief causes of intractable asthma.

(9) Meteorologic and Geologic Factors

The popular clinical belief that sudden meteorologic changes can evoke asthmatic attacks was confirmed by the interesting experimental work of Nelson, Rappaport and Welker²⁵⁰, Preuner²⁵¹ and Courtright and

HOFBAUER L. *Asthma*. Vienna: Springer, 1928.

243. NELSON T. R., RAPPAPORT B. Z. and WELKER W. H. *J. A. M. A.* 100: 138, 1933.

251. PREUNER R. *Z. f. Hyg. u. Inf. kt. on kr.* 121: 559, 1939.

244. VACCAREZZA R. F. and CACCHIARI AVACEDO R. *Ar. Cated. de pat. y clin. tube.* 3: 67, 1941.

Courtright.³⁰⁶ Peters²¹² states that of the nonspecific causes of asthma, weather changes must be considered among the most important. A knowledge of wind direction and the approach of bad weather can help us to understand the patient's symptoms, and often to predict the degree of health he will enjoy during the following days. Petersen and Vaughan³⁰⁷ point out that with rather steady exposure to an allergen of low activity for the individual patient (for example, house dust), weather changes might cause an acute attack and may be a factor in determining fatality. Nelson, Rappaport, and Welker²¹⁰ showed that even when the patient is confined to a room in which the air is filtered and can therefore contain only very few pollens, sudden atmospheric changes (e.g., a sharp barometric fall, a rapid rise in the relative humidity of the air, or rainy weather) can bring on severe attacks. Furthermore, when the humidity is low and the temperature constant, the pollen-asthmatic individual shows more rapid improvement in the pollen-free chamber than when the humidity and the temperature are not controlled. Preuner²¹¹ demonstrated that experimental asthma in guinea pigs is not dependent on temperature, humidity, or atmospheric pressure so long as these factors remain constant on the day of the experiment, while rapid changes in these meteorologic factors increase the average severity of the attack by about 50 per cent. Although Courtright and Courtright³⁰⁶ found that single fixed atmospheric conditions had some effect on the incidence and severity of inhalant sensitization and shock in guinea pigs, they agree that "shifts" in the weather conditions had far more influence. This new field of experimental meteorobiology promises to become highly important in future therapeutic studies. The results of these investigations confirm clinical observations to the effect that asthmatic individuals feel considerably better in a dry warm climate than in a damp environment, and that the most unfavorable conditions are frequent abrupt changes in temperature and humidity. This explains why infectious asthma so often disappears in Arizona, for example, while it is exacerbated near rivers, lakes, swamps, and forests.

High altitudes also have a beneficial influence on asthma. At about 4,000 feet, many asthmatics remain symptom-free as long as the climate is dry and even. This may be due, at least partially, to improved ventilation of the lungs. Furthermore, the decrease in air pressure and in humidity also play an important part. Whether or not high altitudes are beneficial in a given case, can be determined only by a more or less lengthy sojourn in the mountains.

Consideration has been given here only to the direct influence of climate and of high altitudes. The question of the indirect influence of these factors, on the basis of the quantity of pollen in the air and of the fact that fungi flourish far better in damp areas, has been discussed in some detail elsewhere.

Moreover, it must be remembered that cold weather is unfavorable because it tends to promote acute respiratory infections and thus serves to elicit asthma attacks, either specifically (as a result of bacterial sensitivity) or nonspecifically. Lastly, as Duke has pointed out, individuals with hypersensitiveness to cold may have asthma along with other symptoms.

Patients often blame strong winds for the sudden onset of their attacks. The unfavorable influence of wind may be at least partially explained by its cooling effect. Damp air, and particularly fog, tend to elicit attacks. Whether this is attributable to the humidity alone, or whether electric influences (fluctuations of electric potentials) are also involved, has not, as yet, been determined. Another possible explanation may lie in Owens' demonstration that the amount of suspended solid particles in the air is proportional to the fog density, and may be five times as great as that on a clear day. "Industrial fogs" are an exception to the rule; for this condition, observed especially in some English manufacturing centers, has the opposite effect, probably because the acid content of the air counteracts asthma.

Van Leeuwen, Tiefensee, and others have expressed the opinion that the nature of the soil in a given area is of special significance in the production of asthma. They found that clay soil and marshlands increase asthma, and that sandy regions do not. However, the influence of the geologic factor can be nothing

more than an indirect one, since a damp condition of the earth favors the growth of fungi and molds

b) EXCITING FACTORS

Factors tending to produce asthma can, in principle, be of two kinds first, specific factors, or allergens, second, nonspecific factors, or pathergens. The latter category, which includes such diverse stimuli as cold, wind, and irritating gases or vapors, as well as physical exertion and emotional upsets, will not be considered here. The substances that specifically elicit attacks may be divided into two main groups: exogenous allergens, which influence the organism from without, and endogenous allergens, which are formed within the organism.

(1) Exogenous Allergens

It would be practically impossible to list all the substances that have been identified and reported during the course of years. The most commonly encountered exogenous allergens have already been mentioned in Part Two. Here we shall merely make a few general comments concerning the most important allergens.

From the practitioner's viewpoint, the following division by groups, which naturally include only the most important agents, may be helpful. We distinguish asthma due to plants, dust, molds, rusts and smuts, animal substances and emanations, foods, drugs, chemicals, and physical agents. Needless to say, grouping of this kind cannot be absolutely precise, since there may be some overlapping. The trade and professional personnel that are most commonly affected by occupational asthma are bakers, furriers, printers, spinning mill workers, upholsterers, barbers and hairdressers, hat makers, rag sorters, pharmacists, dentists, woodworkers, poultry dealers, coffee, soy, cocoa, and castor bean handlers, jewelers, chromium workers, and refrigerator repairmen (Sternberg and Sorrel²⁰²). Derbes and Winsor²¹⁰⁹ have discussed the mechanism and causative agents of occupational asthma in laboratory workers, food handlers, jewelers, beauticians, pharmacists and chemists, and furriers.

Asthma Due to Plants—Asthma due to pol-

len is discussed separately in chapter XXI. A number of authors, including Rowe¹³ and Peipers, point out that pollens can evoke asthma more frequently than is commonly supposed even at times other than the hay fever season. One of us has seen a severe attack of asthma at Christmas time caused by the pollen of mimosa (*Acacia dealbata*) used to decorate the table.

Furthermore, there are many recorded instances in which the odor of flowers, bushes or trees evoked asthmatic attacks, the same is true of odoriferous fruits. Some doubt exists, on the other hand, as to the nature of the allergen in those cases in which the asthmatic attacks appear while the patient is threshing or loading grains, or sleeping on straw. The possibility of a strictly physical hypersensitivity must be considered in cases of this kind (Urbach and Steiner²⁵⁸). Moreover, as has been instances on page 10, the products of parasites in grains (Ancona⁴⁹) may also be responsible in some occasional instances.

Plants assume especial importance in view of the numerous and widespread instances of hypersensitivity to cottonseed, kapok, orris root, and vegetable gums, as well as to various types of woods. It is necessary to determine in each case whether the wood itself or such contaminants as molds and fungi or even chemical ingredients (particularly resins), represent the causative agent.

Asthma Due to Dust—Since Kern²⁷⁰ and Cooke²⁷¹ first called attention to the significance of dust as an allergen, it has been identified as the causal agent in a constantly increasing number of cases. The size of this group depends, of course, on just what substances—or, rather, just how many substances—one chooses to call "dust." If one includes the dust that promotes asthma in workers in coffee-roasting establishments, in shops and warehouses handling tea, chestnuts, and other products, in carpentry shops and drugstores, as well as in stables, pet shops, and laboratories, this group becomes practically unlimited in extent. Therefore, strictly speaking, the allergen "dust" should be understood to represent only those kinds of dust that, so far as one can ascertain, are not composed of particles of any one specific substance.

Thus, none of the types of dust just mentioned should properly be included; for, in the strict sense of the word, dust should here mean house dust, as well as street dust. This does not imply, of course, that one should not make every effort to determine the origin and components of the dust in each case.

Naturally, house dust is composed of a great variety of substances, including above all the products of animal epidermis, and the content of bedding and upholstered furniture, as well as molds, fungi, and other constituents. When one examines this question more closely, it is interesting to find that many patients react with asthma only to the dust from their own homes or places of work, while others are also hypersensitive to dusts of different origin. In the latter type of case, one must investigate the individual patient, in order to determine whether the reactions are due to the fact that the foreign dusts contain appreciable quantities of the same allergens to be found in the autogenous dust, or whether the reactivity of the patient has become nonspecific or metaspecific. The writers are, therefore, in agreement with Rowe, who holds that there is no such thing as a special house dust allergen per se, but that the effect of the house dust extract is attributable to the sum of the effects of its various components. It seems likely, however, that in a given case one of the components is the chief offender, and that it must, therefore, be identified and removed. In this connection it is interesting to note that Cohen and his associates³⁷³ have demonstrated that cotton linter dust does not act as an allergen until the linters have been stored for several months, and that, moreover, the allergenic action of linter dust is independent of that of cotton dust.

Hypersensitiveness to dust is generally best diagnosed in the following manner. When it has been determined, by means of the environmental tests, that the asthma is directly associated with the patient's presence in a given room, and when no special cause can be discovered there, the dust of the room is collected, according to the instructions on page 200, and cutaneous or bronchial tests are made with extracts of it. If these tests are positive, the furnishings most likely to give off dust (cushions, rugs, hangings, sofa, etc.) are closely examined, in order to obtain an

idea of the allergenic potentialities of these objects. In this manner, one often succeeds in discovering the exact cause and in subsequently achieving a cure, either by removing the guilty substances or by instituting hypersensitization measures.

The same procedure is employed to analyze occupational dust in cases in which the attacks appear not in the home, but in the patient's place of work. Thus, flour and flour modifiers constitute an important cause of asthma in bakers and millers, animal danders in farmers and horsemen, and so on. Some idea of the importance of painstaking investigation of environment is given by the following example. Hanhart²¹⁵⁴ reported the case of a mechanical engineer who suffered asthmatic attacks in a metal foundry, the cause was found to be hypersensitiveness to the lycopodium used to powder the sides of the molds. Another pertinent example is the asthma appearing in goldsmiths, watchmakers, and jewelers, and occasionally found to be due to the dust of octopus gistle (sepia bones) used for polishing (Antona,²¹⁹ Weston⁹⁹⁹).

In view of the fact that almost all testing is done cutaneously nowadays, it should again be mentioned here that numbers of cases are observed in which the patient manifests hypersensitiveness to autogenous dust only on bronchial testing, and in which skin tests are always entirely negative. For further details the reader is referred to page 628.

Molds, Smuts, and Rusts—The allergens of this group have been discussed in some detail in chapter XIII (sec. D). However, the evaluation of the importance of fungi in respiratory allergy is still somewhat subject to controversy. While Waldbott¹⁵⁶³ regards the rôle of fungi as being nothing more than that of a complicating factor, and Browning⁹⁹⁶ concludes that only a few of the skin reactions obtained with molds seem to have real diagnostic significance, Jimenez-Diaz,^{71a3} van Leeuwen,⁷³³ and others consider fungi to represent the chief cause of the asthma that is so common along the coasts of Spain and Holland. In a case of asthma in which the attacks occurred only when the patient returned to his father's house in a suburb of Philadelphia, the

²¹⁵⁴HANHART, E.: Deutsche med. Wchnschr. 60: 1110, 1934

^{71a3}JIMENEZ DIAZ, C., SANCHEZ CUENCA, B., and PETIG, J. J.

Allergy 2: 396, 1932

senior author ascertained the cause to be hypersensitivity to molds. They were found abundantly on the first floor (Figs 263-264). While skin tests with mold extracts were entirely negative an attack of asthma was promptly induced by a bronchial test. In the southeastern portion of the United States, the junior author has seen more than a score of patients with nocturnal attacks due to fungus infested mattresses. Several of the latter yielded a pure culture of *Aspergillus niger* and the remainder mixed cultures of molds. Environmental (night) tests gave clear cut responses and some of the patients manifested huge intradermal reactions. All cases

of slices of cooked white potato in various rooms of the home or place of work. If molds appear they are identified by a mycologist and extracts prepared according to the predominance of the individual species.

Asthma Due to Animal Products and Emanations—The literature contains a great many cases in which hypersensitivity to horses, cattle, sheep, dogs, cats, rabbits, mice, and poultry was definitely proved to be the cause of asthma. Furthermore numerous instances have been observed in which the allergy was only in relation to processed feathers, horsehair or sheep's wool. Lastly there are patients specifically hypersensitive to bees,



EXAMPLES OF MOLDINESS IN HOME REGARDED AS DRY BY MOLD ASTHMATIC PATIENT
FIG. 263 Mold growing on certificate



FIG. 264 Mold growing in unused box

were controlled by discarding the offending mattresses and by hyposensitization therapy.

But regardless of whether fungi are a primary cause of asthma or only secondarily invade the bronchial mucosa, the fact remains that special therapeutic attention is indicated including specific desensitization and intensive treatment with iodides. Lastly it must be stressed that skin tests are frequently of no significance whatever in regard to fungi; positive reactions are often observed when the patient manifests absolutely no clinical sensitivity and vice versa. But the result of bronchial tests (inhalation of suspensions of molds) may be interpreted as specific; the reaction is positive when an attack of asthma ensues within a few hours. Another method introduced by the senior author is the exposure

flies, lice, bedbugs (Sternberg¹⁸, Lahoz and Recatero²⁷⁷) and worms. While some of these patients react only to the epidermal substances of the animals (dander, hair, feathers), the degree of hypersensitivity in others is so great that the mere emanation of a given animal suffices to elicit an attack.

Asthma Due to Foods—According to Peshkin, Rackemann and other observers, foods are the most common causes of asthma in children, while they are responsible for only a small percentage of cases among adults. This may perhaps be explained by the fact that in children the intestines are more permeable to nutritional protein, thereby making possible allergization by ordinarily innocuous foods.

Any ingestant can in principle produce

asthma. The reader is, therefore, referred to the discussion of nutritive allergens on page 295. In occasional instances, the mere odor of the food suffices to evoke an extremely severe attack—e.g., the odor of milk (Creyx), of eggs (Dekker), or of fish (Kaemmerer, Klewitz). According to Sticker, the Polish king Jagello suffered asthmatic attacks from the odor of apples. The writers saw one patient whose hypersensitiveness to fish was of such an extreme degree that she reacted with severe asthma and urticaria after merely passing by a fish store; and the ingestion of 0.2 Gm. of fish propeptan (that is to say, fish protein digested to the peptone stage) elicited similar symptoms. The fact that the attack often appears only many hours after the ingestion of the allergenic food suggests that sometimes not the food itself but certain of its products in digestion may possibly be the allergens responsible.

The search for the allergen in nutritive asthma should never be undertaken by means of skin tests, but by the most cautious administration of the suspected food substance, or preferably by the propeptan diet method (see p. 190).

The statements of patients to the effect that they have food asthma because they suffer attacks following ingestion of certain foods, are often proved by tests to be erroneous, in instances of this kind, the meal merely acts mechanically toward enhancing an attack in a case of asthma based on some other cause. It is not advisable, therefore, for asthmatic individuals to eat too heavily at one time or too soon before retiring for the night.

Asthma Due to Drugs.—The reader will find on page 323 a summary of the drugs known to be capable of evoking asthma. Here we shall merely mention the fact, first pointed out by van Leeuwen,¹¹² that about 10 per cent of all asthmatics react to acetylsalicylic acid (aspirin), even in very small doses (10 to 100 mg.), and that these attacks are usually very severe and of long duration. Since skin tests with aspirin are almost invariably negative, it is advisable to test patients of this kind by placing a small quantity of aspirin under the tongue. As soon as symptoms appear, the aspirin should be rinsed out with vinegar.

Drugs administered parenterally (arsphenamine, sulfonamides, quinine, insulin, and

other glandular extracts) and animal sera also, though less frequently, cause asthma.

Moreover, asthma in druggists, as well as in workers in pharmaceutical establishments, may also be due to lycopodium, ipecac, podophyllin, rhubarb, and digitalis.

Asthma Due to Chemicals.—The reader is referred to page 293 for a discussion of chemicals most commonly responsible for asthma.

Asthma Due to Physical Agents.—Just as urticaria can be elicited by physical agents, so also a number of cases have been recorded, particularly by Duke⁶⁷ in which asthmatic symptoms, usually in association with urticaria, were evoked by cold or heat. To avoid any possible misunderstanding, it must be stressed here that this group does not include those instances in which abrupt changes of temperature, for example, serve to evoke attacks that represent a nonspecific overexcitability of the bronchial neuromuscular apparatus. The group under consideration here includes those patients who never suffer asthma attacks unless they take cold baths or drink cold water as in some cases, or unless they have a rise of temperature as a result of external influences or excitement, as in others. Occasionally typical attacks can also be evoked by sunlight. As for the pathogenesis of these cases, it is as yet uncertain whether a true allergy based on an antigen-antibody reaction or a nonallergic pathergy is involved (for further details, see p. 30).

Lastly, the group of physically induced asthmas also includes the not entirely uncommon cases of mechanical hypersensitiveness of the bronchial mucosa (Michelson), which was proved to be of truly allergic origin by Urbach and Steiner,⁶³ by means of the demonstration that it completely fulfilled the four criteria of Doerr

(2) Endogenous Allergens

According to our nomenclature, there are, in principle, two kinds of endogenous allergens: auto- and hetero-endogenous.

Practically nothing is known concerning the former kind and its connection with asthma. It is possible, however, that this group may include those cases that are associated with some endocrine disturbance—e.g., of the ovaries. This view would seem to be supported by the favorable results sometimes

obtained with premenstrual serum. More over, one might possibly be entitled to arrive at the same conclusion with regard to those patients whose condition improves following eradication of existing constipation, colitis, or other gastro intestinal disorders. In such cases, abnormal digestive products might act as endogenous allergens in the intestines. Lastly, one may also include here those rare instances in which asthma appears only after great physical exertion (Domarus), in these, it might be supposed that the muscles release products to which the organism (and, specifically, the lungs) in time becomes hypersensitive.

Far more is known about the hetero endogenous allergens. These include bacteria and worms. Everything of importance concerning the former has been dealt with in the section on hetero endogenous allergens. As for the causal rôle of worms in asthma, the literature contains a number of conclusive examples, which are discussed in the section named

5. PATHOGENESIS

As is well known, the term bronchial asthma designates a disease characterized by repeated episodes of acute pulmonary emphysema and respiratory distress, resulting from a decrease in the caliber of the lumens of the lower air passages. The more or less sudden onset of the attack is usually accompanied by the formation and laborious expectoration of an extremely viscid bronchial secretion.

According to the present consensus, the attack is brought on partly by a spasm of the bronchial musculature, and partly by the sudden dilatation of the capillaries of the bronchial mucosa, followed by acute swelling of the mucous membranes. The vasodilatation causes the lumens of the smaller bronchi and bronchioles to become so constricted that the passage of air meets with considerable resistance, especially on expiration. Along with the swelling of the mucous membranes there is an increase in secretion, and the resulting viscid mucus occludes many of the bronchi and bronchioles, thus seriously interfering with respiration. Another theory explains the attack as the result of reflex irritation.

According to the studies made by Clerf,²¹⁵⁶

d'Abreu,²¹⁵⁷ and others in regard to the bronchial mucosa during asthmatic attacks the local changes were characterized by swelling, congestion, and edema. The mucosa was found to be covered with adherent mucoid or purulent secretions. In some bronchi, fibrin plugs as also seen at autopsy, were observed.

The microscopic picture generally presents a thickening of the walls of the small bronchi, involving both the muscle tissue and the mucous membrane. The degree of the participation of these two layers varies from case to case, according to the studies of material available. There appears to be an interesting parallel between the histopathology and the clinical course of the disease: patients whose attacks were regularly accompanied by a dry cough—thus, cases in which bronchospasm appeared to dominate the disease—presented at necropsy a microscopic picture characterized by hypertrophic bronchial muscle tissue, as well as in occasional instances by atrophy of the bronchial mucous membranes, however, patients whose attacks were usually accompanied by profuse secretion showed only slight alteration of the musculature, but very marked thickening of the mucosa (Herbst²¹⁵⁸).

The theory that the spasm of the bronchial musculature is caused by an abnormal excitation of the parasympathetics has been discussed in detail on page 569. This view is supported by (1) the results of animal experiments in which it was possible to achieve bronchospasm with acute pulmonary emphysema by stimulating the vagus of an isolated lung, moreover, Ritmann, experimenting with human bronchial muscle tissue removed shortly after death, showed that stimulation of the vagus produced constriction, and of the sympathetic nerve, bronchodilatation, (2) the fact that epinephrine, which acts on the sympathetic nerves, dilates the bronchi, and (3) the fact that atropine, which paralyzes the end organs of the vagus, has a similar effect.

Hurst²¹⁵⁹ has expressed a broader viewpoint in defining asthma as the reaction of an over-excitable bronchial system, including the medullary center, the vagal nerve endings, and the bronchial musculature and mucosa, to

²¹⁵⁶ ANNEU A. L. D. *Lancet* 2: 421, 1940.

²¹⁵⁷ HERBST R. *Asthma bronchiale*. Munich: Gmeln, 1933.

²¹⁵⁸ HERBST A. *Brit. M. J.* 1: 403, 1943.

blood-borne irritants and to reflex and psychic stimuli. This irritable bronchial system, which, according to Hurst, constitutes the "asthma diathesis," is a congenital and often inherited constitutional abnormality.

Years ago, Struempell raised the objection that the assumption of a vagal neurosis as the cause of asthma could not possibly explain the exudative manifestations accompanying the disease. He considered the exudative

and Rigler and Koucky²¹⁶² on the basis of roentgenologic studies using iodized oil. According to these authors, the asthmatic attack is primarily due to a plugging of the bronchi by the mucus resulting from the hypersecretory activity of the bronchial glands (Fig 265). Such plugs have been found on bronchoscopy and removal of them has relieved asthma. On the other hand, not all even of the fatal cases show increased secre-

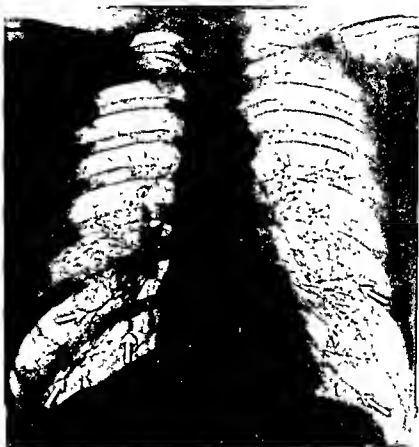


FIG 265 CASE OF CHRONIC ASTHMA

Bronchogram (with lipiodol) showing occlusion of many bronchi by mucus plugs (some indicated by arrows) (Courtesy Dr L. Solis Cohen)

secretory process as the essential factor, and regarding it as playing the same rôle in asthma as in mucous colitis, urticaria, intermittent hydrarthrosis, and migraine. The view that swelling of the mucous membrane, with increased secretion of the bronchi, is of greater significance than the bronchospasm, is also championed by Walzer²¹⁶⁰ on the basis of clinical investigations, and by Steinberg²¹⁶¹

tion of mucus or bronchial plugs. It seems reasonable, therefore, to assume that both spasm of the bronchial musculature and edema of the bronchial mucosa play a part in the pathogenesis of asthma. Moreover, this view received considerable support from more recent investigations that demonstrated the relationship between intramural bronchial nerves, on the one hand, and the smooth

²¹⁶⁰ WALZER, M. *Journal Lancet* 56: 117, 1936.

²¹⁶¹ STEINBERG, B. *J. Allergy* 3: 139, 1932.

²¹⁶² RIGLER, L. G., and KOUCKY, R. *Am. J. Roentgenol.* 39: 353, 1938.

muscle and the mucous glands of the bronchial walls on the other, in mediating motor and secretory control. Furthermore, the nerves of the mucous membranes are also said to function as receptor end organs (Glaser and L. R. Mueller). Autopsy results led Rackemann²⁶ to suggest that in younger patients the symptoms depend mostly on broncho-spasm and perhaps mucosal edema, whereas, when the asthma has persisted for a period of time, the factor of bronchial exudate enters the picture. At first the exudate is thin and not too obstructive, but at any time its character may change until it becomes so viscid, tenacious, and thick as to occlude the lumen and suffocate the patient. A further discussion of this mechanism will be found in the next section.

Lastly, some authors still adhere to the reflex mechanism theory. On the basis of the fact that stimulation of certain areas of the nasal mucous membrane—the so called asthmogenic area of Adam—can by reflex induce a paroxysm of dyspnea, and that such attacks can be stopped by the application of cocaine to this region, the theory of reflex irritation was propounded. Although it cannot be denied that there is such a thing as a vasopulmonary reflex, this mechanism at most applies only to rare cases.

While the above mentioned theories attempt merely to explain the pathogenesis of asthmatic attacks, we shall now consider some of the experimental studies showing that, under certain conditions of exposure, asthma can be induced in both human beings and animals even without the agency of a hereditary element. This can be demonstrated in two ways: (1) by experimental allergization of the bronchial mucosa, and (2) by passive transfer of the hypersensitivity of asthmatic human beings and animals.

Credit for being the first to show that experimental asthma could be induced in animals by repeated inhalation of foreign protein goes to Busson and Ogata²⁷ and to Ratner and his associates.^{28, 29} When animals were allergized by repeated exposure to horse dander, they presented definite respiratory and anaphylactic symptoms, corresponding to those of asthma in man. Moreover, Ratner and

Gruehl^{26a} found that among 20 pigs allergized with horse dander prior to or during pregnancy, the offspring of 18 were also allergized. Similar results in sensitization via the bronchial route have been reported by Alexander, Becke, and Holmes.³¹ Manteufel and Preuner,³² Prausnitz,³³ and Courtright and his associates³⁴ Urbach, Jaggard, and Crisman^{30a} succeeded in sensitizing guinea pigs to ragweed pollen by the bronchial route and in producing typical asthmatic attacks by reexposing them to ragweed pollen inhalation.

Furthermore, the experimental studies of Kallós and Pagel³⁵ are particularly important and illuminating. These authors demonstrated that guinea pigs, when actively or passively allergized, react to inhalations of the finely pulverized homologous antigen with attacks that clinically, roentgenologically, in their response to pharmacologic agents, and even immunobiologically correspond in every respect to bronchial asthma in human beings. Clinically, the animals present expiratory dyspnea associated with coughing. As the attack subsides, there is a discharge of viscid and often thready mucus that has a high content of cells and indeed of eosinophils. In animals that die during the attack, the principal macroscopic finding is an acute pulmonary emphysema of extreme degree, only very rarely accompanied by hemorrhages.

Kallós and Pagel succeeded in eliciting twenty to thirty allergic asthmatic attacks in animals, and thus achieved experimentally a condition analogous to status asthmaticus in man. These animals presented chronic bronchitis, with asthmatic rhonchi in both lungs, and a cough productive of sputum rich in eosinophils. Bronchograms (by means of instillation of lipiodol), taken both before and during attacks, revealed principally occlusion of the smaller bronchi and acute severe emphysema. The obstruction was caused by bronchospasm, by edema of the bronchial mucosa, and by firm plugs of secreted material.

The view that asthma in experimental animals corresponds to that arising spontaneously in human beings is further supported by the pharmacologic response. Atropine, which is an antispasmodic, acts both prophylactically

^{26a} RATNER, B., and GRUEHL, H. L. *Proc. Soc. Exper. Biol. & Med.* 26: 8, 1928.

and therapeutically—a finding that experimentally verifies the favorable clinical results obtained by W. Loeffler. Calcium (in doses of 5 cc. of a 10 per cent solution given eight and four hours before the inhalation) serves as a dependable prophylactic. Lastly, epinephrine has a rapid therapeutic action.

The immunobiologic behavior of the animal is also important. The elicitation of the attacks depends strictly upon the inhalation of the specific antigen. The appearance of asthma following inhalation of the antigen is entirely independent of the antibody content of the blood, and requires only the presence of fixed antibodies in the lungs. Thus, animals sensitized a long time before, and without circulating antibodies in the blood, reacted as strongly as ever. Furthermore, it was shown that the offspring of an allergized mother also responded to inhalation of the antigen used to sensitize the mother. Further, both types of intra-uterine transfer of allergy were observed—namely, active and passive allergization.

Histologic examination by Bergstrand¹⁶⁴ and Pagel¹⁶⁵ yielded findings that correspond to the available reports on chronic bronchial asthma in human beings. The picture is dominated by the enormous eosinophilic reactions in the walls of the smaller bronchi, which leads to the formation of eosinophilic granulomas and marked alterations in the bronchial wall, including edematous swelling and thickening of the basement membrane. Lastly, eosinophilic pneumonia can be found, the cells being present in the lumen of the alveoli. As a result of the pathologic changes in the bronchi, there occur such alterations of the air content of the parenchyma as emphysema alternating with extensive atelectases, often associated with consolidation or even hepatization.

It is interesting to note that considerable agglomerations of eosinophils are sometimes observed in the spleen.

Lastly, Kallós and Pagel have shown that the inhalation of a fine spray of a histamine or acetylcholine solution will elicit attacks that correspond, symptomatically, to those of allergic asthma in human beings. However, the histologic and immunobiologic findings are

such that these substances cannot be regarded as the decisive factors in the production of the tissue reaction considered typical of bronchial asthma.

As for the unintentional production of experimental asthma in human beings, the reader is referred to the material presented on page 10.

6. PATHOLOGY

In contrast to the period prior to 1931, when the literature included only a few autopsied asthma cases with microscopic examination (33 instances according to Coca¹), the past decade or so has brought forth a rather impressive quantity of material. Thus, Lamson and Butt¹⁶⁷ reported 48 additional necropsies, Hilding¹⁶⁸ 39, Rackemann¹⁶⁹ 10, Colton and Ziskin¹⁷⁰ 9, Thieme and Sheldon¹⁷¹ Bases and Kurtin¹⁷² and Craige¹⁷³ 7 each, Chafee and his associates¹⁷⁴ 6, Unger¹⁷⁵ 5, Pratt¹⁷⁶ 4, Jorgensen¹⁷⁷ 3, and Michael and Rowe¹⁷⁸ 2, in addition to quite a few others who each performed 1 autopsy. These cases are not to be confused, however, with those of persons who, as Thieme and Sheldon¹⁷¹ have aptly put it, "died with, but not of, asthma"; nor of those who died as the direct result of therapeutic measures, especially administration of morphine. Cohen and Rudolph¹⁷⁹ alone have described postmortem findings in 5 cases in which morphine apparently was responsible for death.

There is, unfortunately, no agreement as to the number of autopsies of cases of asthma reported in the literature. Some are rejected as having had asthma, but not having died during an attack, and others are not regarded as being examples of true bronchial asthma. Thus, including his own cases, Craige¹⁷³ estimates the number of genuine cases to 1941 as 59. Rackemann¹⁶⁹ reported necropsies on 50 cases

¹⁶⁷ LAMSON, R. W., and BUTT, E. M. *J. A. M. A.* 108, 1843, 1937.

¹⁶⁸ HILDING, A. C. *Ann. Otol., Rhin., & Laryng.* 52, 5, 1943.

¹⁶⁹ RACKEMANN, F. M. *J. Allergy* 11: 147, 1940.

¹⁷⁰ COLTON, W. A., and ZISKIN, T. *J. Allergy* 6: 347, 1937.

¹⁷¹ THIEME, E. T., and SHELDON, T. M. *J. Allergy* 9: 246, 1938.

¹⁷² BASES, L., and KURTIN, A. *Arch. Otolaryng.* 36, 79, 1942.

¹⁷³ CRAIGE, B. JR. *Arch. Int. Med.* 67: 399, 1941.

¹⁷⁴ CHAFFEE, F. R., ROSS, J. R., and GUNN, E. M. *Ann. Int. Med.* 17, 43, 1942.

¹⁷⁵ UNGER, L. *South. M. J.* 38: 513, 1945.

¹⁷⁶ PRATT, H. N. *New England J. Med.* 223, 626, 1940.

¹⁷⁷ JORGENSEN, J. V. *Biblot. f. Imper.* 128: 217, 1936.

¹⁷⁸ MICHAEL, P. P., and ROWE, A. H. *J. Allergy* 6: 150, 1935.

¹⁷⁹ COHEN, M. B., and RUDOLPH, J. A. *J. A. M. A.* 98: 1864, 1932.

¹⁶⁴ BERGSTRAND, H. *Acta path. et microbiol. Scandinav.* 5, 261, 1928.

¹⁶⁵ PAGEL, W. *Virchows Arch. f. path. Anat.* 286, 590, 1937.

with asthma as the presenting symptom, but found pathology which he regarded as typical of asthma in only 27 of them to these he added from the literature up to 1944 a total of 55 cases which fulfilled the clinical and autopsy criteria of the disease Lamson, Butt, and Stickler²¹⁶⁰ added to their original series²¹⁶⁷ 86 autopsies of "fatal asthma," but many of these patients admittedly had other diseases which simulated the clinical symptoms of asthma, and should perhaps have been designated as suffering from paroxysmal dyspnea

There is no really pathognomonic pathologic picture of asthma, but certain changes are so commonly observed that they may be regarded as characteristic Grossly, autopsy after a patient dies in a paroxysm invariably discloses the known signs of emphysema when the thorax is opened, the lungs do not collapse, but are voluminous and distended, the diaphragm is situated low, the borders of the lungs extend over the mediastinum, and finger imprints remain depressed In cases of long standing, emphysematous blebs are not uncommonly observed as secondary changes The lungs are often pale or grayish in color with a fine bluish mottling, which is uniform throughout The peribronchial and mediastinal lymph nodes are often enlarged The cut surface of the lungs often presents rather small atelectatic areas Many of the bronchi are filled with plugs of thick tenacious mucus and fibrin as well as cellular elements and debris The heart sometimes shows hypertrophy of the right ventricle Microscopically the walls of the small bronchi are generally thickened, this thickening involves both the muscle and the mucous membrane, but the degree of involvement of each of these layers varies considerably from case to case In this respect, there seems to be an interesting parallel, according to Herbst,²¹⁶⁸ between the microscopic picture and the clinical course of the disease (see above) The smaller bronchi and alveoli may be more or less enlarged depending on the degree of emphysema

Pneumonia is a frequent terminal complication at autopsy The cardiac findings will be considered in a separate section below

On microscopic examination the *bronchial muscles* frequently show the effects of work hypertrophy Occasionally, as illustrated in FIGURE 265, the lumens of the bronchioles are completely obliterated for brief distances, after which one observes small saccular dilations (Brul²¹⁶⁹) Although these changes might be interpreted as anatomic proof of the bronchospasm theory of asthma, it must not be forgotten that the same changes are observed in chronic bronchitis, the hypertrophy of the musculature may be due, therefore, to overwork of the muscles resulting from prolonged strenuous coughing

The *mucous membrane* presents narrowed and elongated ciliated epithelial cells, the lower parts of which often appear stretched out and nearly threadlike Here and there these cells are cast off and replaced by cuboidal cells that consist at some places of one and elsewhere of several layers Between the epithelial cells there are exceedingly numerous goblet like cells that in some areas outnumber the epithelial cells, and that virtually may replace the normal columnar ciliated cells—an instance of metamorphosis in the pathologic sense Hilding²¹⁶⁸ emphasizes this loss of ciliary function as the essential cause of death, since it produces a profound disturbance in the normal mechanism by which bronchial secretions and exudates are removed The basement membrane of the epithelium is usually hyalinized and thickened Moreover, the mucous membrane is hypertrophied, leading to the formation of longitudinal folds on the surface of the membrane, beneath these, there are transverse folds resulting from the contraction of the hypertrophied circular muscles The longitudinal folds may be developed to such an extent and may be so close together that they narrow the lumens of the bronchioles down to threadlike slits

The *submucosa* shows dilatation and overfilling of the blood vessels Between the capillaries there occur cellular infiltrations composed of lymphocytes and particularly of eosinophilic leucocytes Hemorrhages into the mucosa may also be encountered The mucous glands are abundantly filled with mucus

²¹⁶⁰ LAMSON R W, BUTT E M and STICKLER M J *Allergy* 14: 396 1943

²¹⁶⁹ BRUL M, HILKEMAND P, and DELARUE J *Ann d anat Path* 12: 769 1935

Within the *bronchioles* themselves, one finds varying amount of exudate, the quantity apparently depending on the type of asthma present. The secretion is viscid, mucinous, and thready, and contains, in addition to Curschmann spirals and Charcot-Leyden crystals, numerous cellular components consisting of cast-off epithelial cells, eosinophilic and other leucocytes, and erythrocytes, as well as fibrin. The inspissated secretions occlude the air passages and are adherent to the walls, suggesting that death occurs from asphyxia

(5) Hyperplasia and hypersecretory activity of the goblet cells of the mucosa,

(6) Hypertrophied and overactive mucous glands and goblet cells with excessive mucus in the bronchial lumen, and often plugs of thick tenacious mucus and fibrin in the medium- and even large-sized bronchi,

(7) Thickened submucosal layer, the vessel walls may be thickened,

(8) Eosinophilic infiltration of the mucosa, and at times of the musculature, the tracheo-bronchial lymph nodes, and the peribronchial tissues,



FIG 266. PATHOLOGY OF BRONCHIAL ASTHMA

Photomicrograph of medium-sized branch bronchus from asthmatic patient showing large mucus plug filling bronchial lumen (Mu), partial loss of ciliated epithelium, diffuse inflammatory cellular infiltration, largely eosinophilic, in submucosa (Et), and marked hypertrophy of bronchial muscle (Br M).

(Courtesy Dr. B. A. Gouley)



FIG 267. PATHOLOGY OF BRONCHIAL ASTHMA

Photomicrograph of same patient as in Fig. 266. Note mucus plug (Mu), hyalinization of basement membrane of mucosa (H), irregular loss of ciliated epithelium, hypertrophy of bronchial muscle (Br M).

(Courtesy Dr. B. A. Gouley)

In summary, the pathologic picture in patients dying of asthma is characterized by a majority of the following features:

(1) Lobular or generalized emphysema,

(2) Increased thickness of the bronchial wall with narrowing of the lumen, due to hypertrophy of the bronchial musculature (especially in chronic cases) or hypertrophy of the mucosa, sometimes leading to an in-folding of the mucosa;

(3) Thickening and hyalinization of the basement membrane of the medium-sized bronchi;

(4) Enlargement or sacculation of the bronchi;

(9) Partial loss of epithelial lining of bronchi, and frequently metamorphosis

Many of these lesions are illustrated in Figs. 266 and 267, the sections having been taken from a woman aged 53 who died of asthma.

The present writers have had the opportunity of examining 10 cases post mortem and histologically. In agreement with Lamson and Butt,²¹⁶⁷ Rackemann,²¹⁶⁸ Hilding,²¹⁶⁹ and many others, they are of the opinion that death from asthma is due chiefly to the formation of tough sticky plugs that occlude the bronchi and lead to suffocation. Asphyxial death in asthma, then, results from bronchial obstruction based on the following factors: overproduction and retention of mucus, muscu-

lar contraction of the bronchi, and mucosal edema

It is of special significance that almost all of the demonstrable pathologic changes observed in human beings who died of asthma were also found by Kallós and Pagel²¹ in connection with experimental asthma in animals, as described in the preceding section. Consequently a rather characteristic pathologic picture of asthma emerges. However, the same findings, except for the tissue eosinophilia, can also be produced by such terminal conditions as cardiac decompensation and pneumonia, or by complicating diseases such as bronchiectasis.

Lastly, the following interesting findings in occasional instances have been reported. In 7 cases of asthma, Harkavy²¹⁸² found perivascular eosinophilic infiltrations, resembling those of periarthritis nodosa, in nodules present in the subcutis. Bahrmann,²¹⁸³ Rackemann and Greene,²¹⁸⁴ and Trasoff and Scarf²¹⁸⁵ had previously described necrosis of the media in the larger arteries, as well as degeneration of the elastica, and marked infiltration of the adventitia and intima with eosinophile cells—i.e., the pathologic picture of periarthritis nodosa. Other instances of similar lesions, including intimal thickening of the small vessels, necrotizing arteritis, endarteritis obliterans, fibrosing arteritis, and granuloma formation, particularly of the heart, lungs, and serous surfaces have been reported by Harkavy²¹⁸⁶ and Rackemann²¹⁸⁷ as found at necropsies of asthmatics. In Baker's²¹⁸⁸ case, the vessels of all organs were involved. It is suggested that the periarthritis nodosa is rather a pathologic picture occurring in the progress of asthma than a disease in itself. The changes are reversible, according to Harkavy.²¹⁸⁸ Patients of this type may be distinguished from the usual asthmatic case by a high blood eosinophilia (at least 25 per cent), transient pulmonary eosinophilia, and electrocardiographic changes. The recogni-

tion that periarthritis nodosa is encountered not uncommonly in association with severe types of asthma suggests that a lesion of the blood vessels is a part of the fundamental process (Harkavy²¹⁸⁹). On the other hand, there are reports that periarthritis nodosa may occur in patients without any symptoms of allergy.

Debre,²¹⁹⁰ Harkavy,²¹⁸² Chafee²¹⁷⁴ and their associates found that asthmatic individuals may present marked eosinophilia of the bone marrow, during both the attacks and the symptom free intervals.

Bahrmann²¹⁸³ and Chafee²¹⁷⁴ found diffuse myocarditis with eosinophilic infiltration in fatal cases of asthma.

A unique case of fatal bronchial asthma showing an "asthmatic reaction" in an ovarian teratoma was described by Thomson.²¹⁹¹ An evidently asphyxial asthmatic death followed an injection of morphine. At autopsy nearly all the pulmonary lesions mentioned above were found, along with the presence of mucus in some of the alveoli. In addition, an ovarian teratoma existed showing typical respiratory epithelium. The latter showed "asthmatic" changes similar to those in the bronchi, such as eosinophilic infiltration, Charcot Leyden crystals, and a thickened basement membrane.

Finally, Hagen²¹⁹² discovered pathologic changes in almost all the cervical ganglia removed from 7 patients with severe bronchial asthma. These included hypertrophic glomerulus like formations, vacuolation, and granular degeneration in the bodies of the ganglia and the processes, and an increase in multinuclear ganglion cells.

7 SYMPTOMATOLOGY

Clinically, asthma may be broadly defined as a recurrent dyspnea, generally paroxysmal in nature, accompanied by wheezing and usually by coughing. It may take any of six clinical forms: (1) respiratory oppression, causing a subjective sense of tightness in the chest and objective difficulty in taking a deep

²¹⁸¹ HARKAVY J. Arch Int Med 67: 709 1941

²¹⁸² BAHRMANN E. Virchows Arch I path Anat 296: 277 1936

²¹⁸³ RACKEMANN F. M. and GREENE J. E. Tr A Am Physicians 54: 112 1939

²¹⁸⁴ TRASOFF A. and SCARF M. J Allergy 11: 277 1940

²¹⁸⁵ HARKAVY J. ibid 14: 507 1943

²¹⁸⁶ RACKEMANN F. M. New England J Med 232: 704 1945

²¹⁸⁷ BAKER L. A. Ann Int Med 17: 223 1942

²¹⁸⁸ HARKAVY J. J Mt Sin Hosp 8: 592 1942

²¹⁸⁹ DEBRE R. LAMY M. and BERNARD J. Compl rend Soc de Biol 123: 679 1936

²¹⁹⁰ THOMSON J. G. J Path & Bact 57: 213 1945

²¹⁹¹ HAGEN E. Deutsche Ztschr f Chir 259: 667 1942

breath; there is no wheezing during this stage, (2) the "wheezing or pre-attack" stage (a term applied by Peshkin¹¹²) often erroneously diagnosed as bronchitis; in this the symptoms are mainly referable to the various asthmatic rhonchi heard in the chest on auscultation and the dyspnea may be so mild as to escape attention; (3) the attack, representing the peak of the asthmatic syndrome, (4) status asthmaticus; this is, as the name implies, a prolonged asthmatic paroxysm; (5) chronic asthma, in which the patient is never entirely free from dyspnea, not even in the intervals between frank attacks, in this type many nonspecific stimuli, particularly physical exertion, will often lead to paroxysms; (6) certain "masked" forms in infants and children.

The first two forms require no further discussion. They are observed either as the forerunners of an initial seizure or, not too infrequently, during the intervals between acute attacks, and can, therefore, be diagnosed as asthmatic manifestations only if the patient has previously had asthma or exhibits it subsequently.

a) THE ASTHMATIC ATTACK

The most important stage is the asthmatic paroxysm, presenting a clinical picture that is most alarming, both to the patient and to the observer. The attack generally does not begin in full force, but gradually grows more and more intense so that the patient finds it increasingly difficult to breathe, until finally he struggles painfully for air and thinks that he is suffocating. The respiratory rate is accelerated, as is the pulse rate. Cyanosis is often present, and may sometimes be quite marked. This is rarely the result of cardiac insufficiency; it is due to the fact that the bronchi and bronchioles are occluded by mucous plugs, thus preventing adequate oxygenation of the blood. Almost invariably expiration and less frequently inspiration are accompanied by high-pitched whistling, rumbling or sonorous sounds plainly audible from some distance and called the "wheeze." Both phases of respiration are accomplished with difficulty. The accessory muscles of res-

piration come into play, but succeed in elevating only the upper part of the thorax. They become very taut, and contractions in the jugular, epigastric, and intercostal regions are visible during each inspiration. In the neck one can see the straining, during inspiration, of the sternocleidomastoids, scaleni, and other muscles. Particularly characteristic, however, is the difficult, noisy, long-continued expiration, in the course of which the abdominal muscles become tense and rigid. In summary, the respiratory disturbance in asthma is essentially an expiratory dyspnea. Despite this fact, most patients describe the distress as an inability to draw a deep or satisfying breath. Many patients complain of a sense of impending death in severe attacks.

The attack is often preceded by certain preliminary manifestations that Hofbauer¹¹³ has appropriately termed the aura. Many patients feel a strong desire to sneeze, followed by copious nasal secretion and frequent sneezing or nasal obstruction so intense that they cannot breathe through the nose. Some mention olfactory hallucinations, still others feel depressed or complain of a "burning" or obstructing sensation within the chest. In some instances, the patient yawns with striking frequency. Moreover, the attack is sometimes preceded by severe itching of the skin, and even by urticarial manifestations. Occasionally the precursors of the attack involve the gastro-intestinal or urinary tracts: cases of diarrhea or of the voiding of great quantities of nearly colorless urine have been observed. These symptoms merit strict attention, since prompt recognition will enable the physician to apply measures that may prevent the full-blown manifestations.

In many cases the attack is preceded by a desire to cough or by spells of coughing, practically no sputum can be raised despite frantic efforts. In others, the coughing first appears after the paroxysmal dyspnea has begun to subside, or it may interrupt the attack, thereby serving to aggravate the shortness of breath. Frequently the expectoration of a "plug" or two of viscid grayish mucoid sputum seems to terminate the attack. If coughing is severe, particularly after a meal, vomiting may supervene.

¹¹² PESHKIN, M. M. discussion to Clem, N. W. J. *Allergy* 10: 2:5, 1939.

When the paroxysms begin at night the patient sometimes awakens with the dyspnea at its height. What alarms him most is the dreadful feeling of suffocation that is not alleviated by the most strenuous exertion but is rather exacerbated by his vain efforts. This is due to the fact, as shown by pneumograms taken during attacks, that expiration is prolonged and inadequate. When suffering their first paroxysms, patients usually jump out of bed and throw open the windows. They soon learn by experience, however, that they can best combat the shortness of breath by remaining absolutely quiet and motionless. There is a characteristic position these patients assume: the body is in the sitting position but bent forward, the head is drawn in between the shoulders, and the chest is in the position of maximal inspiration, the hands are braced on the edge of the bed or chair, and the arms held rigidly in extension fixing the shoulders. The entire body is often covered with sweat, and the face is pale and sometimes swollen. The employment of the accessory muscles of respiration for hours at a time often causes a sensation of soreness in the lower thorax in the region of the insertion of the diaphragm as well as in the attachments of the abdominal musculature.

Sooner or later (after hours, days, and sometimes even weeks) the period of time depending on the nature of the allergen or pathergen involved, the attack subsides and the patient is entirely relieved of his respiratory difficulties as well as of the accompanying anxiety. However, the borders of the lungs do not always return to normal immediately, moreover, the rhonchi often persist for some time despite the absence of symptoms.

The attacks very commonly occur at night. The reason for this is as yet unknown. It may be that the physiologic domination of vagal tonus during sleep favors the onset of the attack. Possibly it is the accumulation of bronchial secretions—since these are not removed during sleep—that irritate the bronchi and thus leads to an asthma paroxysm. In some instances, the nocturnal occurrence of the attacks can be explained on the basis of hypersensitiveness to some substance in the bedding or to some other allergen in the bedroom.

One occasionally sees asthmatic equivalents

in the form of rhinopathy, laryngotracheitis, tracheobronchitis or of a persistent whooping cough like paroxysmal cough. That these conditions of the mucosa properly belong to the category of asthma is shown by the presence of numerous eosinophils in the secretions, and particularly by the fact that they are observed to alternate with typical asthmatic paroxysms. In addition, certain skin manifestations, such as neurodermatitis, infantile dermatitis, and urticaria, may also occur as equivalents.

Many patients feel that the position of the body has a definite effect on the relative intensity of an attack: that is, when they lie supine, even in the daytime, paroxysmal dyspnea appears, while they remain symptom free so long as they sleep in a sitting position with the head bent forward and possibly resting on a table (Wiehler,²¹⁴ Urbach and Loew²¹⁰³). There may be an explanation for this relationship in the observation of Danielopolu and Carmiol that in labile individuals, the supine position produces a vagal stimulation that can be controlled with atropine. Urbach and Loew²¹⁰³ found this conditioning of symptoms by position mostly in cases of tuberculo-allergic asthma.

The frequency of the attacks is extremely variable. Sometimes they occur almost nightly, then there may be symptom free intervals of weeks or months. For this reason, it is hazardous to predict the course of the disease.

b) STATUS ASTHMATICUS

When a patient suffers from continuous attacks or from successive paroxysms at such short intervals that he does not have time to recover from one attack before the next appears, the condition is described as status asthmaticus. Sufferers in this state present a picture of the greatest misery and distress. Their dyspnea and cyanosis are intense. In such cases the cough is totally unproductive and therefore ineffective. Aside from great physical fatigue, the patient usually has headache, frequently accompanied by nausea and vomiting, pallor, sweating and marked tremor, the latter symptoms, however, may be due to the frequent administration of epi-

nephrine demanded by this condition, and required in constantly increasing dosage since it becomes less and less efficacious. The pulse is rapid, weak, and sometimes irregular. If it is impossible to control the status asthmaticus, a more or less marked degree of stupor ultimately sets in, probably attributable to cerebral anoxia. These attacks may last for days, and even for a week and longer. The urine then commonly contains albumin and casts, and sometimes traces of sugar as well. When the continuous paroxysms persist for days, the patient frequently has fever without localized pulmonary signs, lasting three or four days, and disappearing after the dyspnea has subsided (Clarke^{213c}). Other cases of this kind present frank pulmonary consolidation, with the physical findings of pneumonia. Finally, death from anoxemia, cardiac failure, or exhaustion may intervene.

c) CHRONIC ASTHMA

Status asthmaticus is not to be confused with the chronic state of asthma. The latter is present not only in those cases in which the patient is continuously exposed to the causative exogenous allergen or pathogen for some time, but also in bronchitis asthma—i.e., in individuals with chronic bronchitis who become hypersensitive to the bacteria in their own bronchi. The chief difference between status asthmaticus and chronic asthma is that severe paroxysms are relatively rare in the latter, though there is continuous respiratory distress of rather mild degree. These patients practically never enjoy complete freedom from dyspnea, even during the intervals. Dyspnea and wheezing are exacerbated particularly by exertion and emotional stress. Chronic asthma is rather often associated with the asthenic habitus (Fig. 268).

Rackemann^{213e} has recently emphasized the occurrence of depletion and debilitation in the course of prolonged asthma, as evidenced by loss of strength and weight. Such a change in general health can be due to the asthma, or it can be primary (resulting from pneumonia, operation, emotional disturbance, chronic fatigue) and lead to asthma. In consequence, a vicious cycle may ensue. Depletion often

occurs in what Rackemann classifies as "intrinsic" asthma, but also appears in asthmatic bronchitis. Its treatment demands, in addition to the proper allergic therapy, general measures such as good nursing, rest, adequate diet, and perhaps sunshine. Rackemann feels



FIG. 268 ASTHENIC HABITUS FREQUENTLY SEEN IN CHRONIC ASTHMATICS

that nervous and psychic elements accompanying depletion are secondary to the impairment of general health.

d) MASKED FORMS OF ASTHMA IN INFANTS AND CHILDREN

Since the clinical characteristics of asthma in childhood differ rather markedly from those in adult life, they require separate consideration. This subject will be discussed in chapter XXXIV.

e) THE INTERVAL BETWEEN ATTACKS

Patients who have had asthma for some time show, in their symptom-free intervals,

^{213c} CLARKE, J. A., JR. - *J. Allergy* 4, 481, 1943

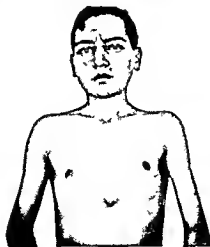
^{213e} RACKEMANN, F. M. - *J. Allergy* 16, 136, 1945.

signs of pulmonary emphysema most clearly manifested in the limited respiratory mobility



FIG 269 BOWING OF BACK AND INCREASED ANTERO POSTERIOR DIAMETER DUE TO CHRONIC ASTHMA

fixed in the position of inspiration with the ribs and sternum abnormally elevated and the upper thoracic inlet nearly horizontal. The shoulders are also elevated and the spine shows an increase in the dorsal curvature (FIG 269). Moll¹⁹⁷ called attention to the fact that the thoracic deformity in asthma characterized by increased anteroposterior diameter (FIG 269) dorsal kyphosis and anterior pigeon breast deformity (FIGS 270 271) differs from the barrel chest of true emphysema. The latter may be interpreted as indicating the presence of emphysema due to chronic bronchitis. Funnel breast deformity is occasionally seen in children (FIG 272). The deformity of the thorax found in children with asthma and resulting from the abnormal muscle pull on the developing thoracic cage has been termed asthmatic pseudorickets by Bock²¹⁹³. In appearance it differs from true rickets in that the upper transverse diameter of the thorax is greatly enlarged giving an inverted pear like configuration to the trunk. In true rickets caused by a normal muscle pull on an abnormally soft thoracic



PIGEON BREAST WITH VERY PROMINENT XIPHOID PROCESS IN ASTHMATIC BOY
FIG 270 Frontal view



FIG 271 Lateral view

of the lower borders of the lungs. As a rule these patients also present a paravertebral dullness at the level of the third and fourth thoracic vertebrae generally more marked on the right side than on the left. This is caused by enlargement of the hilar structures. Furthermore there is usually a change in the contour of the chest which is more or less

cage the upper transverse diameter is greatly narrowed.

When not too far advanced both the emphysema and the thoracic changes can retrogress with a return almost to normal after lengthy periods of rest. Approximately the

MOLL H H Lancet 1 12 1937
* Bock J Ztschr f Kinderh 63 579 1942

same is true of the bronchitis, which is so marked during the attack, and which subsides completely only after the first few paroxysms. As a rule, the patient gradually develops chronic bronchitic manifestations, persisting even during the intervals. The chronic irritation of the lower respiratory passages, according to Hofbauer,²¹⁹ is due to the fact that asthma patients almost always

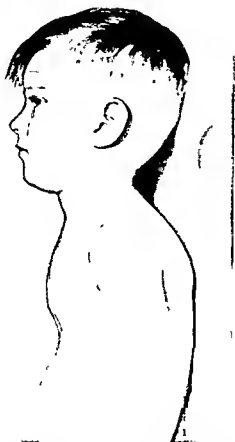


FIG. 272. FUNNEL BREAST IN FIVE YEAR OLD BOY WITH ASTHMA OF THREE YEARS' DURATION

breathe through the mouth, or at least do so whenever there is a rise in their oxygen requirements (as when climbing stairs), in order to satisfy their increased air hunger.

f) CLINICAL COURSE

The course of a given case is naturally largely dependent on whether the asthma is of exogenous or endogenous etiology. In the former case, a recurrence of the attack can be prevented if the causative agent can be eliminated or avoided (e.g., in hypersensitiveness to animal dander or to a food).

But when one is dealing with an endogenously caused asthma of infectious or bronchitic type, the circumstances are quite different. Here too, of course, there may be periods during which the patient seems to be completely free of symptoms. But the slightest chill or draught will cause a flare of the underlying infection and thereby elicit an attack. At the beginning, the symptom-free intervals are longer, but later, a nonspecific irritability of the bronchi supervenes, and all kinds of nonspecific stimuli, such as cold wind, rain, change in the weather, smoke, lengthy conversations, physical exertion, fatigue, excitement, anger, and even laughing, can act as the trigger mechanism. This transition is known as "pathergization." When the action of an exogenous excitant is of long duration, or when a patient with endogenous asthma is unable to cough up the masses of material clogging his bronchi, status asthmaticus appears. After many recurrences of attacks of infectious asthma, the disease tends to enter the chronic stage.

Asthma is to be regarded as a serious condition, chiefly because it frequently incapacitates the patient for a long time. Furthermore, the emphysema and the resulting cardiac decompensation are not to be taken lightly. Nevertheless, it is noteworthy that asthmatic individuals live to a comparatively old age. Although the morbidity is high, the mortality is relatively low. However, the available statistics for the latter are misleading, since asthmatic patients are usually recorded as dying of secondary cardiopathy or pneumonia. Every physician who has occasion to treat many severe cases has a number of deaths every year that are primarily caused by the asthma itself; but of these patients, only relatively few die in status asthmaticus. The mortality is considerably higher among patients of advanced age than among younger individuals. However, in severe cases, the prognosis in the case of infants and young children is likewise serious. Deaths in this age group have been reported by Stolte, Ehle, Engel, and others.

All in all, the intelligent statement of the famous Frenchman, Trousseau, still applies: "Asthma is not a grave disease, but a serious affliction."

8 COMPLICATIONS AND SEQUELAE

Partial or complete occlusions of the bronchi based on the mechanisms considered in the sections of pathogenesis and pathology are directly responsible for many of the complications of asthma including emphysema

pathogenesis should include allergic management control of infection by appropriate measures bronchodilating drugs and aerosols bronchoscopic dilatation rest mild sedation environmental control and where necessary postural drainage



FIG 273 ASTHMA OF MANY YEARS DURATION

Extreme emphysema long vertical heart and prominent hilar (penbronchial) markings

atelectasis bronchiectasis spontaneous pneumothorax mediastinal emphysema and infectious inflammatory processes superimposed upon the site of the occlusion or distal to it Mansmann and Osmond²¹⁹⁵ refer to the narrowing of the diameter of the bronchial lumen irrespective of mechanism as bronchiostenosis employing the term in a broader sense than that in which it is used below The treatment of this condition depending on the

EMPHYSEMA

The overexpansion of the lungs demonstrable during and immediately after every attack of asthma retrogresses more or less promptly afterward In time however the condition becomes chronic (FIG 273) either because the tissues of the lungs eventually lose their elasticity after frequent overdistention or as many observers now hold because of the associated bronchitis asthma as a result of which smaller or larger bronchi are practically obstructed by mucus or swelling

²¹⁹⁵ MANSMANN J A and OSMOND L H Pennsilvania M J 49 513 1946

of the mucosa. The question is still controversial. However, the personal factor is an important one: some individuals develop a permanent emphysema of the lungs in a surprisingly short time, while others present normal lungs after having recovered from status asthmaticus of long duration. Moreover, there is not necessarily any direct relationship between the severity and duration of the asthma on the one hand, and the degree of pulmonary emphysema on the other. One

caused by insufficient oxygenation of the arterial blood and a lowered vital capacity.

Chronic emphysema predisposes the asthma patient to chronic bronchitis and thereby to secondary bacterial infections, and so institutes a vicious circle.

PULMONARY RUPTURE

When the emphysema is especially severe, blebs at the surface of the lungs or at the hilum may rupture. Whether this results in



FIG. 274. SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA IN CHILD

Mottled appearance of soft tissues of neck and chest wall is due to contained air.
(Courtesy, Dr. L. Solis Cohen)

occasionally encounters severe cases with slight emphysema, and mild cases with an extreme degree. The available figures concerning the incidence of emphysema in asthma are contradictory. Zdansky observed it in 57 per cent of his cases, Dillon and Gurewitsch, in 35 per cent (as compared to 25 per cent among controls). Manges and Hawley, on the other hand, observed marked emphysema in only 1 per cent of asthmatics.

The symptoms produced by associated pulmonary emphysema are chiefly cyanosis and dyspnea; they are present even when the patient is free of asthma, and are particularly marked on exertion. The cyanosis is probably

subcutaneous emphysema (FIG. 274), characterized by crepitation on digital pressure over the swollen area, or a spontaneous pneumothorax, depends on whether pleural adhesions exist, and on their location and extent, as well as on the precise site of the pulmonary rupture and its anatomic relationship to the great vessels. When there is a free pleural space, pneumothorax develops; but when adhesions are present, air escapes from the ruptured lung into the subcutaneous tissue. In some rare instances, both developments can take place at the same time (Faulkner and Wagner²⁵⁹⁹). Further observations were con-

tributed by Jeffrey and Marlatt²⁰⁰ Rey et al²⁰¹ and Skinner²⁰²

According to Derbes Engelhardt and Sodeman²⁰³ search of the literature reveals only 21 cases of spontaneous pneumothorax in asthma although the condition is probably somewhat commoner. This infrequency in the face of the thinned visceral pleura in emphysema is probably explained by a progressive decrease in the negativity of the intrapleural pressure. Even bilateral spontaneous pneumothorax has been observed as a complication of asthma (Davidson and Brock²⁰⁴). When the pneumothorax is secondary to mediastinal emphysema the roentgenogram shows a fine sharp line running parallel to the cardiac border. The principal symptoms of pneumothorax are severe dyspnea, marked cyanosis and thoracic distress. The prognosis is excellent under bed rest and sedation, thoracentesis for the removal of air should be strictly reserved for cases of tension pneumothorax with resultant embarrassment of respiration (Trowbridge⁶⁵). Once healing is established the resorption of the nitrogen remaining in the pleural cavity may be speeded by the inhalation of 100 per cent oxygen (Derbes et al²⁰³).

Rosenberg and Rosenberg²⁰⁵ found that in 1938 only 18 cases of subcutaneous emphysema had been described in the world literature although more recently reported cases bring the total to at least 29 (Schwartz²⁰⁷ Francis⁶⁸ and Fong and Rospide⁶⁹). The condition may involve not only the neck but may extend to the face, upper extremities, thorax, abdomen and even the legs. Spontaneous subcutaneous emphysema in the course of an asthmatic attack is due to multiple small ruptures of the bases of the marginal

type of alveoli, the air then entering the pulmonary interstitial tissues, traveling along the vascular sheaths to the mediastinum and as a result of the increased pressure escaping along the carotid perivascular sheaths to the subcutaneous tissues of the head, neck or elsewhere. It is self limited to four days to two weeks and the prognosis is excellent with conservative therapy consisting of oxygen inhalation, sedation and control of the asthma. Only very rarely is incision or needling of the emphysematous blebs necessary.

Mediastinal emphysema may also complicate the course of asthma accompanying pneumothorax or subcutaneous emphysema or occurring independently. The intense substernal pain may simulate that of myocardial infarction although many differential features exist. The diagnosis is based on the characteristic physical findings and the pathognomonic roentgen appearance.

PULMONARY ATELECTASIS

Pulmonary atelectasis is relatively frequent in severe cases and is attributable to the obstruction of small or medium bronchi. Accordingly the lobular form is usually the one encountered here although the lobar type (Fig. 27c) is sometimes seen. Massive atelectasis has rarely been described in this connection. The onset of atelectasis is in general associated with fever and always with marked dyspnea. The presence of tenacious mucus completely or partially obstructing the lumen can frequently be confirmed by bronchoscopy. Atelectasis is not infrequently observed in children (Friedman and Molony⁷⁰). Cole, Nalls and Buis⁷¹ reported four cases of asthmatic atelectasis simulating pneumonia. The occurrence of pulmonary atelectasis during attacks was also reported by J. A. Clarke, Jr., H. B. Wilmer and others. Physical and roentgenologic examinations revealed the typical picture of a collapse of the lung just as seen postoperatively. In cases of this kind bronchoscopic aspiration of the obstructing masses of secreted material will often terminate the attack.

²⁰⁰ JEFFREY W. G. S. and MARLATT D. C. *Canad. M. A. J.* 39: 171, 1938.

²⁰¹ REY A. J., REY J. C. and LERTORA E. *Rev. a. genit. de tube c.* 5: 167, 1939.

²⁰² SKINNER H. H. *J. Ped.* 18: 117, 1941.

²⁰³ DERBES V. J., ENGELHARDT H. T. and SODEMAN W. A. *Ann. Allergy* 3: 2, 1945.

²⁰⁴ DAVIDSON M. and BROCK R. C. *Proc. Roy. Soc. Med.* 37: 157, 1944.

²⁰⁵ TROWBRIDGE M. Jr. *A. J. Int. Med.* 73: 460, 1944.

²⁰⁶ ROSENBERG L. and ROSENBERG J. *Am. J. M. Sc.* 195: 682, 1938.

²⁰⁷ SCHWARTZ E. *J. Allergy* 16: 279, 1944.

⁶⁸ FRANCIS N. *Ann. Allergy* 2: 342, 1944.

⁶⁹ FONG E. G. and ROSPIDE P. C. *Sem. med.* 52: 46, 1944.

⁷⁰ FRIEDMAN T. B. and MOLONY C. J. *Am. J. D. Child.* 58: 237, 1939.

⁷¹ COLE D. B., NALLS W. L. and BUIS L. J. *Virginia M. Month.* 7: 505, 1941.

of their patients with bronchiectasis although their material was unusual in consisting largely of asthmatics who had moved to Arizona.

The development of bronchiectasis is probably to be explained on the basis of an initial basal allergic bronchitis which in time causes an atelectasis, this is followed after a variable period by the bronchiectatic dilatation. Hence it has been suggested that in order to prevent bronchiectasis bronchoscopy should

be performed (Chapman and Hoskins²² and others). As a rule bronchiectasis in asthmatic patients is of the cylindric type (Chapman and Hoskins²²). In connection with this procedure it should be pointed out that prior to each instillation of iodized oil the patient must be tested for possible hypersensitiveness to iodine and poppyseed or rape seed oil by application of a drop of the iodized oil to the nasal or buccal mucosa before administration intratracheally. While the al-

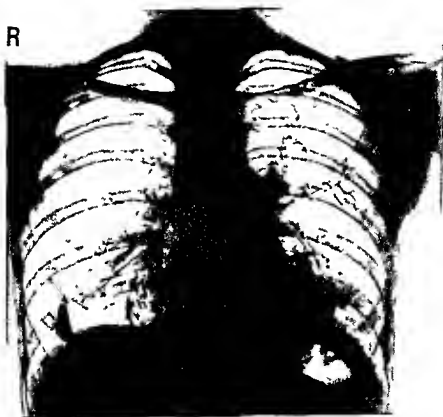


FIG 216 LIPIODOL BRONCHOGRAM OF CHRONIC ASTHMA WITH BRONCHIECTASIS

(Courtesy, Dr L. Solis Cohen)

be performed for the purpose of establishing drainage as soon as it is apparent that an area of lung is atelectatic.

It has become increasingly evident that it is possible by means of bronchography with iodized oil to demonstrate the presence of both the cylindric (FIG 276) and sacculated (FIG 277) types in asthmatics when other methods fail (Balyeat and associates²³ Cho-

lergy is usually in relation to the iodine occasionally one of the oils mentioned is the causative agent. This precaution will guard against severe anaphylactic conditions and even fatal reactions such as have been observed. The necropsy findings of such a case were recently described by Mahon²⁴. Other untoward effects include asthma, urticaria, transitory swelling of the parotid and submaxillary

²³ BALLEAT R M, SEYLER L E and SHOEMAKER H A
Radiology 24 303 1935

²² CHOROF R. Am J Dis Child 52 882 1941
CHAPMAN J and HOSKINS H. Am Rev Tuberc 43 12 1941
²⁴ MAHON C S. J A M A 130 194 1946

glands, and papular, pustular, bullous, or hemorrhagic skin eruptions.

The presence of bronchiectasis is suggested clinically by an increase in the quantity of sputum, the characteristic separation of the sputum into three layers, and its becoming fetid. Furthermore, there is sometimes asymmetry of the lower portion of the thorax, and râles may or may not be present on auscultation, or may be inconstant in the same patient.

plication of asthma in severe forms. The stenosis is a definite localized stricture-like narrowing of a bronchus, probably primarily inflammatory and not allergic in nature. It occurs most frequently in the lower posterior portions of the lungs. The physical signs of bronchostenosis consist chiefly in the suppression of breath sounds and impairment tactile fremitus. The roentgenologic findings are those relating to atelectasis, occasionally complicated by those characteristic

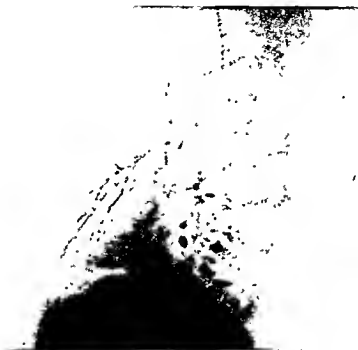


FIG. 277 CHRONIC ASTHMA WITH BRONCHIECTASIS
Lateral view, showing both saccular and cylindric dilations of bronchi
(Courtesy Dr. L. Solis-Cohen)

In order to avoid diagnostic and therapeutic errors, it should be borne in mind that atypical or virus pneumonia may be followed by pseudobronchiectasis, in which dilatation of the bronchi may persist for weeks or months. However, this is thought to be a reversible process, requiring no therapy, although it is sometimes difficult to differentiate from early or dry bronchiectasis.

BRONCHOSTENOSIS

According to Prickman and Moersch,²²² bronchostenosis is a relatively common com-

plication of asthma. There is often fever of 101 to 103 F., lasting several days. The sputum is mucopurulent and sometimes streaked with blood. Treatment consists of bronchoscopy, with dilatation of the stenosed bronchus, followed by aspiration of the retained secretions.

OTHER COMPLICATIONS

The occurrence of infectious pneumonia in the course of asthma, particularly as a terminal event, has been mentioned above. Moreover, secondary infection of an atelectatic area of lung not infrequently gives rise to pneumonia. In addition, in asthma of short duration, es-

²²² PRICKMAN, L. E., and MOERSCH, H. J. *Ann Int Med* 14, 387, 1940.

pecially in infants and young children a type of pneumonitis occurs that can be regarded in a sense as part of the clinical picture of the asthmatic attack. Transient pneumonic infiltrations (Loeffler's syndrome) also sometimes complicate the course of this disease. These last two conditions will be discussed on pages 660 and 662.

Pleurisy is rather rarely a complication of asthma. It can be the result either of a concomitant tuberculosis or of other pulmonary diseases such as pneumonia in the asthmatic patient. An erroneous diagnosis is sometimes made when the pleuritic pain is mistaken for muscular soreness due to paroxysms of coughing.

Multiple spontaneous fracture of ribs has been reported by Oechsli¹ and Waldbott^{2, 35} and is probably due to intense coughing during an attack. The fractures appear always to occur in an oblique line extending from a point near the costochondral articulation of the fourth rib and the ninth rib in the midaxilla.

A case of *cystic degeneration of the lungs* was described by Waldbott^{2, 35}. It is assumed that during the years of severe cough and dyspnea the patient blew out an emphysematous area near the periphery of the lung first causing a pneumothorax and later a cystic degeneration.

9 ASTHMA AND RHINOPATHY

Until a very few years ago it was generally held that the nasal or sinus diseases so commonly demonstrable among asthma patients represented one of the principal causes of asthma. Today however many prominent allergists and rhinologists including Rackemann^{19, 3} Hansel³⁶ and Kern and Schenck¹⁹²⁹ are of the opinion that asthma, rhinopathy and sinus disease are concomitant manifestations of the same condition in different sites and that all of them are attributable to the same underlying causal factors.

In 1 074 cases of asthma Rackemann and Tobey¹⁸⁹⁰ found rhinopathy in 17 per cent in the extrinsic group and in 10 per cent in the intrinsic group—a total of 27 per cent.

We¹⁸⁹¹ studied this important question in 379 asthma cases. (Pollen asthma was for obvious reasons excluded from consideration.)

The findings were that rhinopathy is frequently encountered in cases of asthma (38 per cent). In almost half of these cases the rhinopathy had appeared simultaneously with the asthma; in these the two conditions were invariably found to be due to the same agent—*allergen* or *pathergen*. And when the rhinopathy had its onset shortly before or after the asthma (by less than two years) the two conditions were usually found to be due to the same cause. However in instances in which the rhinopathy first appeared many years before or after the development of the asthma the two conditions were likely to be due to different causes (Table 52).

TABLE 52—*Time Relationship between Onset of Asthma and Rhinopathy*

Onset of Rhinopathy	Of 145 Etiology with Asthma	Of 50 Different Etiology	Total
Before asthma	22	31	53
Simultaneous with asthma	68		68
After asthma	5	19	24
Total	95	50	145

There were 145 cases of demonstrable rhinopathy among 379 cases of asthma. Rhinopathy was found with the greatest relative frequency in the pathergic group (53.8 per cent) but of these cases less than half were demonstrably due to the same cause as the asthma. Among the specific allergic asthmas on the other hand where the incidence of rhinopathy was also very high (46.8 per cent) the overwhelming majority of the cases of rhinopathy were found to be due to the same allergen as the asthma.

With regard to sex there was a slight preponderance of rhinopathy among the male cases—39.7 per cent as compared with 36.3 per cent among the female.

Rhinopathy merits far more consideration than it has as yet received. This condition is often the forerunner of asthma, constituting a preliminary stage that can be of variable duration. In this early phase the allergy is frequently monospecific and treatment should be easier and more effective than when the asthma has really become manifest. More

over, the early treatment of rhinopathy is an important element in the prophylaxis of asthma. At this point, it would be well to recall the well-known fact that hay fever, which is essentially a rhinopathy due to pollen, is often the forerunner of pollen asthma.

In cases in which nasal and bronchial manifestations appear simultaneously, it can be assumed that both conditions are caused by the same agent. Hence, the septal membrane may be advantageously used as a test area, and also as a site for treatment. Thus, Urbach and Wiethe⁷³⁴ successfully employed intramucosal injections of the specific allergen as well as of peptone. Hallermann⁷³⁵ has confirmed the efficacy of this procedure. In cases of rhinopathy and asthma in which the allergen cannot be identified, Jacquelin and Bonnet⁷³⁶ undertook desensitization by means of intramucosal injection of autogenous serum.

The incidence of nasal polyps in cases of asthma is high (30 per cent according to Kern and Schenck¹⁹²). It is interesting to note, in this connection, that marked polyp formation may occur in asthma without any other clinical or rhinologic evidence of rhinopathy (Urbach and Gottlieb¹⁹³).

Reports of the incidence of sinus disease in association with asthma vary considerably, ranging from 12 per cent (Bullen) to 89 per cent (Kelly; Weille). However, it must be recalled in this regard that apparently healthy and nonallergic individuals also present a high incidence of gross nasal pathology or of sinus disease. Thus, in 50 nonallergic controls, Kern and Donnelly²²⁶ found clinical or roentgenologic indications of sinus disease in 72 per cent—as compared with 80.5 per cent in asthmatics. This high incidence of sinus involvement in normal subjects, however, is confined to certain sections of the country, particularly the eastern seaboard. As might be anticipated from these findings, the literature contains many reports to the effect that submucous resections and sinus and polyp operations do not benefit asthma in the majority of cases.

10. ASTHMA AND CARDIOPATHY

In nearly every case of severe or prolonged asthma, particularly in middle-aged and el-

derly patients, the problem arises as to whether the heart is affected and, if so, whether primarily or secondarily. This subject has attracted considerable attention in the last few years, as can be seen from the extensive literature.

Rational therapy depends upon the answers to each of the following questions: (1) Is there any cardiopathy in the given case? (2) If so, is it the result of the bronchial asthma, or (3) is the cardiopathy of an unrelated etiology?

It is not always a simple matter to determine clinically whether cardiac disease exists in a patient with bronchial asthma, since physical examination is often unreliable because of the accompanying emphysema. Hence the advisability of employing electrocardiography, X-ray studies, circulation times, and spirometry, in order to obtain an objective evaluation of the status of the lesser circulation.

In asthma, there is not infrequently a moderate cyanosis of the lips that is due merely to a dilatation of the labial capillaries and is therefore without clinical significance. The pulmonary type of cyanosis, observed much less frequently, manifests itself as a more general bluish discoloration of the face and of the distal portions of the extremities, and is to be interpreted as an expression of cardiopulmonary failure. It constitutes a delicate indication of early cardiac decompensation in the asthmatic subject.

Clinical observations²²³ on 452 of our own cases disclosed an accentuation of the second aortic sound in 27 patients, and of the second pulmonic sound in 13 cases, with tachycardia (rate over 120 to 130 per minute) in 5. The X rays showed an enlargement of one or both ventricles of the heart in 32 patients, congestion of the pulmonary circulation in 10, and 1 instance of dilatation of the aorta.

Electrocardiograms should be taken not only in the asthma-free interval but also after effort, and, if possible, during an asthmatic attack. Such studies by the authors²²⁶ revealed a high incidence of lesions of the myocardium, predominantly caused by anoxia. It also seems likely that there is a direct in-

²²³ URBACH, E., LOEW, A., and GOTTLIEB, P. M. *Cardiologia* 6: 13, 1942.

²²⁶ KERN, R. A., and DONNELLY, J. C. *J. Allergy* 3: 172, 1952.

involvement of the cardiac vessels in the allergic reaction

Electrocardiographic study of the heart in asthma has only recently been attempted. Kahn²⁹⁷ was one of the first to take electrocardiograms in the asthma free intervals. In a series of 50 cases he found 10 cases of right ventricular preponderance, 21 of left ventricular preponderance and only 19 normal electrocardiograms. Somewhat similar results were obtained by Unger²⁹⁸, Colton and Ziskin¹⁰, Hochrein and Dinischiotu²⁹⁹ and Schiller, Colmes and Davis³⁰⁰ except that right axis deviation was much more commonly found than left. Some of the patients showed evidence of myocardial damage such as inverted T waves or disturbances of conduction including arborization block. On clinical examination the hearts of such patients are almost always considered normal. On the basis of his studies Hochrein expressed the view that a pulmonary circulatory disturbance—mediated either through a bronchospasm or possibly through reflex action—is the primary basis of asthma. On the other hand some authors found no electrocardiographic abnormality that could be interpreted either clinically or electrocardiographically as indicative of cardiac damage. The statements of various authors concerning axis deviation are somewhat at variance and this may be partly explained by the fact that the same criteria are not always used for the evaluation.

Harkavy and Romanoff³⁰¹ made electrocardiographic studies on 50 patients during and after an attack. Twenty of them showed changes in the auricular and/or ventricular complexes during the asthmatic paroxysm. Among these the electrocardiographic abnormalities had disappeared in 9 cases when the attack was over. Mainzer and Krause³⁰² found altered electrocardiographic tracings during the asthmatic paroxysm in half of their patients. They consider it to be due to myocardial anoxia brought about by insufficient oxygen saturation of the arterial blood

and by reduced coronary circulation resulting from hemodynamic disturbances or nervous stimuli (increased arterial pressure in the pulmonary circulation increased vagal tone).

In 209 of our cases electrocardiograms were taken before digitalis or strophanthin therapy with the results shown in Table 53.

In 9 cases there occurred a depression of the ST segments in lead II on effort during an attack, whereas for the asthma free interval the findings were normal. We consider this as evidence of a temporary anoxia of the myocardium.

We have accepted as criteria of myocardial involvement or dysfunction the following deviations in the electrocardiogram: (1) prolonged a v conduction time, (2) low voltage

TABLE 53. *Abnormal Electrocardiographic Findings in 209 Cases of Asthma*^{302a}

Type of Electrocardiographic Abnormality	No. of Cases	Percentage
Myocardial involvement during asthma free intervals	62	29.0
Myocardial involvement only after effort	5	2.4
Myocardial involvement only during attack	4	1.9
Right axis deviation	2	1.0
Left axis deviation	1	0.5
Sinus tachycardia	1	0.5
Total	5	35.3

of the initial deflection or arborization block or bundle branch block, (3) depression of the ST segment, low, flat or inverted T waves, particularly in the absence of axis deviation or QRS changes, and (4) abnormally high P waves in leads II and III.

The findings mentioned under (1), (2) and (3) would lead one to think of arteriosclerotic and hypertensive etiology, while those under (4) and those under (3) which include abnormalities in leads II and III point to the pulmonary factor.

However we wish to call attention to the fact that not all myocardial abnormalities in asthmatics, especially in older people, are primarily caused by the bronchial asthma. Such changes are often due to coexistent arteriosclerosis or hypertension.

²⁹⁷ KAHN, M. H. *Am. J. N. S.* 173: 555, 1927.

²⁹⁸ UNGER, L. *J. Allergy* 2: 17, 1930.

²⁹⁹ HOCHREIN, M. and DINISCHOTU, G. T. *Ztschr. f. klin. u. allg. forsch. Med.* 145: 1939.

³⁰⁰ SCHILLER, I. W., COLMES, A. and DAVIS, D. *New England J. Med.* 228: 113, 1943.

³⁰¹ HARKAVY, J. and ROMANOFF, A. *J. Allergy* 12: 40, 1941.

³⁰² MAINZER, F. and KRAUSE, M. *Cardiologia* 5: 261, 1941.

The following cases are illustrative of these electrocardiographic findings.

Case 1. N. S., age 30 years, female.

History: Chronic asthma with emphysema

Findings: Small vertical heart

Electrocardiogram (FIG 278) Mild right axis deviation and some prominence of P waves in lead II and III.

Course Death six months after electrocardiogram was taken

Case 3 J. M., male

History Asthma for several months

Findings Moderate degree of emphysema and, at times, crepitant râles at both bases Blood pressure 174/104



FIG 278 ELECTROCARDIOGRAM IN CASE 1

(Courtesy Dr H Roesler)

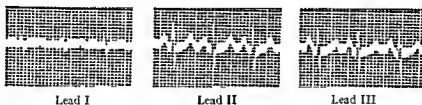


FIG 279 ELECTROCARDIOGRAM IN CASE 2

(Courtesy Dr H Roesler)

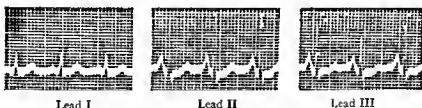


FIG 280 ELECTROCARDIOGRAM IN CASE 3

(Courtesy Dr H Roesler)



FIG 281 ELECTROCARDIOGRAM IN CASE 4

(Courtesy Dr H Roesler)

Case 2 R. F., age 42 years, male

History Asthma in childhood, dyspnea on exertion for past seven years, wheezing on exertion Strongly positive tests with chicken feathers and certain foods

Findings: Marked degree of emphysema Small vertical heart, with prominence of conus of right ventricle Normal venous pressure and circulation time

Electrocardiogram (FIG 279): Low voltage of initial deflection in lead I and prominent P waves in leads II and III.

Electrocardiogram (FIG 280) Moderate tachycardia prominence of P waves in leads II and III, and slight depression of ST segments in leads II and III

Case 4 L. A., age 65 years, male

History Chronic asthma with emphysema and bronchiectasis

Findings Marked emphysema, râles at both bases.

Blood pressure 140/100 Normal circulation on time Heart not enlarged Leucocytosis fever

Electrocardiogram (FIG 281) P wave deflects on prominent and also notched in leads II and III Voltage of initial deflect on at lower limit of normal ST segments slightly depressed T wave on base line in lead I positive and of slightly lower voltage in leads II and III

The evidence of cardiac involvement during the asthmatic attack corresponds closely to the findings of Kallos and Kallos-Deffner¹⁹ and of Ewert and Kallos²²² who made electrocardiographic studies of animals with experimental asthma before during and after the asthmatic attack Such studies showed that even mild asthmatic attacks were accompanied by disturbances of rhythm of production and conduction of the impulse and of coronary circulation These were attributed by Kallos to anoxia There is also evidence that the coronary vessels may be directly involved in the allergic reaction Eiselsberg²²³ and Criepe²²⁴ reported definite electrocardiographic changes in animals in anaphylactic shock The same findings were demonstrable during acute asphyxia and are indistinguishable from those in acute myocardial infarction in human beings Like wise conduction disturbances reduplication of the second pulmonic sound and atrioventricular block have been demonstrated during allergic attacks in man (Melli Kaemmerer)

In addition there are many interesting studies concerning hypertrophy of the ventricle In 1929 Harkavy²²⁵ expressed the opinion that asthmatics with emphysema acquire a right ventricular hypertrophy In chronic cases this is followed by decompensation death in such patients is accordingly a cardiac death Harkavy also found a definite eosinophilic infiltration in the walls of the pulmonary arteries leading to the assumption that the allergic reaction may produce symptoms of hypersensitiveness not only in the lungs but also in the vascular system

In autopsies on asthmatics Sotier^{2,37} Colton and Ziskin²¹⁷ and MacDonald²²⁶ found

enlarged hearts and hypertrophy or hypertrophy and dilatation of the right ventricle in a large percentage of cases Sotier employs the term pulmonary hypertrophy implying that the cardiac hypertrophy is induced by stasis in the lesser circulation Schiller Colmes and Davis²³⁰ found that cor pulmonale was more common than generally realized Of 12 patients who died after having had asthma for more than six years 5 died in congestive failure and predominant hypertrophy of the right ventricle was found at autopsy in 4 of these Cor pulmonale hypertrophy and dilatation of the right heart was present in 12 cases of a series of 50 necropsies reported by Rackemann²³¹ and in 5 it was considered to be the cause of death Other findings reported less often include fatty infiltration or patchy fibrosis of the myocardium endocardial sclerosis and narrowing of the lumens of the coronary arteries On the other hand there are several reports in which the heart was found to be normal (Michael and Rowe Kountz and Alexander Wright)

The recent investigations of Weiss and Kleinbart²²⁸ corroborated from the roentgenologic standpoint by Roesler²³² showed that the mechanism and clinical picture of bronchial asthma are very similar to those of paroxysmal cardiac dyspnea On this basis they established a disease picture of cardiac emphysema due to chronic left ventricular hypertrophy—which by analogy is the counterpart of cardiac asthma due to acute left ventricular failure Swineford and Magruder²³³ and Smith and Paul²³⁴ reported the relatively frequent occurrence of left ventricular failure in asthmatics According to Plotz²³⁵ some forms of left ventricular failure produce a paroxysmal dyspnea indistinguishable by symptoms physical signs or therapeutic response from bronchial asthma

Even in patients with normal electrocardiograms and negative physical examinations the possibility of a cardiac disturbance—

²²² EWERT B and KALLOS P *bid* 2 147 1938

²²³ EISELSBERG K P *Klin Wchschr* 13 619 1934

²²⁴ CRIEPE L H *discuss on to Harkavy and Romanoff* ²²⁵

²²⁵ HARKAVY J J *Alergy* 1 136 1930

²²⁶ SOTIER A *Fortchr a d Geb d Roentgenstrahl en* 58 89 1938

²²⁷ MACDONALD I G *Ann Int Med* 6 253 1932

²²⁸ WEISS E and KLEINBART M *Pennsylvania M J* 41 1026 1938

²²⁹ ROESLER H *discuss on to Weiss and Kleinbart* ²³⁰

²³¹ SWINEFORD O Jr and MAGRUDER R G *South M J* 30 829 1937

²³² SMITH F M and PAUL W D *Ann Int Med* 12 58 1938

²³³ PLOTZ M *bid* 13 111 1939

perhaps only functional—cannot be excluded. For we have become more and more convinced (see below) that properly conducted cardiotherapy, primarily with intravenous aminophylline and strophanthin, may lead to astonishing improvement of the asthmatic condition, and should therefore be attempted as a matter of principle in severe cases.

It would be misleading, however, to report only the average incidence (17 per cent) of cardiopathy in our series, because the frequency, depending upon the pathogenesis of the asthma, varied from zero in the specific-allergic group to 27 and 29 per cent in certain pathergic types and in bronchitic and tuberculo-allergic asthma. The explanation would seem to lie in the fact that these groups suffer from more or less chronic dyspnea with resulting strain on the heart, while specific-allergic asthma is more or less an acute condition of short duration.

Even from this clinical study, it seems very probable that the cardiac condition is to be regarded as due to the asthma. But one should not overlook the fact that a considerable percentage of patients with bronchitic asthma have reached an age at which sclerotic vascular processes might have led to myocardial involvement independently of the asthma. It should also be noted that we have never observed asthma in conjunction with endocarditis or associated valvular defects.

Before discussing the clinical characteristics of cardiac involvement to be found in association with bronchial asthma, we shall briefly consider cardiac asthma, the symptomatology of which resembles that of bronchial asthma.

Cardiac asthma, as pointed out by Scherf and Boyd,²²⁴ is primarily a central dyspnea without marked pulmonary congestion. This central respiratory disturbance is caused by a functional inadequacy of the left ventricle, not demonstrable in the heart itself, but manifest in the disturbed blood supply to the medullary centers. Even though spontaneous paroxysmal dyspnea is the most significant and striking symptom in cardiac as well as in bronchial asthma, a careful analysis of the clinical symptoms will usually permit a differential diagnosis. Cardiac asthma is often as-

sociated with a sense of suffocation and oppression, accompanied by a fear of impending death.

The most direct method for differentiation between bronchial and cardiac asthma is on the basis of circulation times, which show decreased blood velocity in the pulmonary circuit in the paroxysmal dyspnea of cardiac origin. Arm-to-tongue times (saccharine, calcium, magnesium, decholin) and arm-to-lung times (ether) may be quickly and accurately determined at the bedside (Cottrell and Cuddie²²⁵). Fishback and his associates²²⁶ inject a 10 per cent sodium fluorescein solution that gives rise, under ultraviolet light, to a distinctive greenish glow in the palpebral conjunctiva, thus obviating the uncertainty of subjective end points. In healthy subjects the arm-to-tongue circulation time varies between ten and fifteen seconds. It is not prolonged in uncomplicated asthma during or between attacks, and may be shortened. However, if bronchial asthma is complicated by ventricular failure, the circulation time will exceed eighteen seconds and may even be doubled or trebled, both during and between attacks. The same lengthening of the time will be found in cardiac asthma, owing to left ventricular failure or general congestive heart failure.

Much more frequently than the need for the differential diagnosis as between bronchial and cardiac asthma, however, the question arises as to whether bronchial asthma is complicated by heart disease, particularly in cases arising on the basis of an old emphysema, usually associated with a chronic bronchitis. In this connection, Roesler²²⁷ has pointed out that the cardiac silhouette in the presence of emphysema has certain characteristic features. Quite frequently such patients will exhibit dyspnea independently of their asthmatic attacks, and the dyspnea will be increased on exertion. Often this symptom receives too little attention as an evidence of cardiac injury, because the pulmonary insufficiency is attributed to the marked emphysema. The fact that the dyspnea of the emphysematous

²²⁴ COTTRELL, J. D., and CUDDIE, D. C. *Brit. M. J.* 1: 10, 1942.

²²⁵ FISHBACK, D. B., GUTMAN, S. A., and ARNIMSON, E. B. *Am. J. M. Sc.* 203: 335, 1942.

²²⁶ ROESLER, H. *Clinical Roentgenology of the Cardio-vascular System*, ed. 2, Springfield, Ill. Thomas, 1943.

²²⁷ SCHERF, D., and BOYD, L. J. *Cardiovascular Diseases Their Diagnosis and Treatment*. St. Louis: Mosby, 1939.

bronchitic patient is of expiratory character points to its pulmonary origin. In addition to the diminution of the respiratory surface another important factor is the interference with the capillary pulmonary circulation owing to the disappearance of the alveolar septa causing decreased oxygenation of the venous blood.

In emphysematous patients therefore there is always a certain degree of pulmonary insufficiency the degree of which corresponds to the status of the basic disease. On the whole we are inclined to attribute the decreased exercise tolerance and the respiratory distress on exertion that appears with advancing age more to pulmonary than to cardiac failure. Of course, the increasing burden on the pulmonary circulation in progressive emphysema will gradually lead to excessive strain on the heart. In asthmatic patients however in whom both the attacks and the associated bronchitis hasten the development of the more advanced forms of emphysema this cardiac inadequacy will develop much sooner than in cases of ordinary senile emphysema. It is most difficult however to determine the time at which cardiac involvement is superimposed on pulmonary insufficiency in each individual case because the first and for a long time the only symptom of the former—the dyspnea—is not characteristic and is only too frequently associated with emphysema due to bronchitis.

Since the dyspnea of chronic asthma that is often associated with severe emphysema is frequently of a complex nature cardiac therapy should always be instituted in addition to specific therapy directed to the asthma for it is difficult to diagnose the earliest manifestations of cardiac involvement. However an analysis of the different types of dyspnea may be possible to some degree by means of spirometry. In noncardiac emphysema the vital capacity is the same in the upright and the recumbent position while in emphysema with cardiac failure our experience has shown the vital capacity is less in the recumbent position than in the upright. This agrees with the clinical occurrence of orthopnea in heart failure while emphysematous patients with normal hearts, although dyspneic on effort, have

no more respiratory embarrassment in the horizontal than in the sitting posture.

If the right heart failure is acute the patient will show a generalized very deep cyanosis because of the acute hemodynamic insufficiency resulting in marked diminution of the volume of blood delivered from the right ventricle to the lungs. Directly associated with the cyanosis that develops from anoxemia there is an extremely severe dyspnea in these patients present even in rest. Such acute fulminant failure of the right heart may then lead to a fatal termination.

Hyperacute right failure of such sudden onset is generally rare. Much more frequently the inadequacy develops with a more gradual congestive failure. The following case is a typical example of the splendid results of cardiotherapy in bacterial allergic asthma.

A C. 60 years of age had gripe and pneumonia five years previously followed by his first asthmatic attacks—at first occurring only once a month later more frequent and prolonged. He worked as a saddle maker and had formerly had attacks of sneezing and coryza due to the leather dust. He was a tall emaciated man with severe peripheral cyanosis and long narrow thorax. The diaphragm was at the level of the first lumbar vertebra and poorly mobile. Auscultation revealed a prolonged expiratory phase with numerous moist and sonorous râles over both lungs. There was a forceful cardiac impulse with the apex beat palpable in the sixth interspace the sounds were of good quality the rhythm regular the radial artery slightly rigid. The systolic blood pressure was 125. He had an enlarged liver. No edema was present.

The electrocardiogram revealed slight axis deviation and evidence of dysfunction. Dyspnea as continuous and frequently changed into typical asthmatic attacks which responded promptly to epinephrine. Only after cardiotherapy (daily intravenous injection of strophanthin 0.1 mg. increasing to 0.5 mg. along with aminophylline 0.24 Gm. in 10 cc. of 50 per cent glucose) was there any great improvement or any considerable decrease in the cyanosis.

We have discussed above the occurrence of heart disease as the direct result of asthma. But heart trouble may develop independently of asthma. As a rule one has to deal with an affection of the myocardium on the basis of coronary arteriosclerosis. As is known this disease may develop insidiously without symptoms or objective signs. Frequently however, there will be cardiac pain thoracic oppression, and angina pectoris. We have observed that asthmatics complain more frequently

of anginal symptoms than other subjects of the same age—especially during attacks—so that the possibility of a pathogenetic relationship between bronchial asthma and angina pectoris must be considered. The pain in the latter condition is thought to be related to cardiac anoxia. As oxygenation of the lungs is interfered with during the asthmatic attack, causing an oxygen deficiency in the coronary arteries, anoxia of the heart might develop on this basis alone, while the increased cardiac activity during the attack raises the oxygen demand. But we have also observed the development of painful cardiac sensations during the attack in younger asthmatics in whom there are no reason to assume the presence of organic heart disease. An objective basis for this theory of acute anoxia is furnished to some extent by electrocardiograms taken during such an attack. Voit and Landes²³ came to the same conclusion.

It is quite understandable that such frequent disturbances of oxygenation of the myocardium must, in the course of years, lead to permanent changes. Consideration must also be given to the possibility that the smooth musculature of the vessels may become allergized on the basis of persisting infection of the respiratory mucosa, such as is usually present in asthma of long duration. Then one might interpret the acute insufficiency during the asthmatic attack not only as a hemodynamic phenomenon but also as an allergic manifestation in the coronary vessels, analogous to the asthma.

Asthmatic attacks may lead to stenocardia, while severe forms of stenocardia accompanying coronary thrombosis may appear under the guise of asthmatic symptoms. This is especially true if the dyspnea produced by the stenocardia is of the reflex type, i.e., hyperacute and paroxysmal in nature. If a reflex secretion of the bronchial mucosa (the so-called asthma "humidum") is associated with the stenocardia, the clinical picture will resemble an asthmatic attack even more closely, as is sometimes seen in acute coronary occlusion. However, an analysis of the symptoms, together with the cardiac and electrocardiographic findings, will soon reveal the true cause of the respiratory disturbances.

Naturally, disease of the left heart may develop without preceding anginal difficulties. Cardiac failure first manifests itself in dyspnea on effort, but, in contrast to the situation in asthma, usually shows no paroxysmal character. This dyspnea corresponds objectively to pulmonary congestion. The latter escapes clinical detection at its onset, being demonstrable only roentgenologically, and has proved to be one of the subtlest symptoms of the combination of bronchial asthma with cardiac disease. It is still unknown how often this combination may be associated with bronchial asthma developing on the basis of emphysema. In these relatively rare cases a differential diagnosis of the two forms of asthma may be exceedingly difficult, because the paroxysmal cardiac dyspnea will also manifest itself as an expiratory dyspnea, owing to the spastic tendency of the bronchial musculature produced by the bronchial asthma. A distinction between the two forms of asthma is therefore impossible because of the identical mechanisms of both—for the originally specifically allergized lungs of the patient will in time react to nonspecific stimuli also. The release of an asthmatic attack in this manner is called pathergic asthma in our terminology. One may assume that the respiratory center, overstimulated by the disturbance in the greater circulation, may act acutely, with the lung as its end organ. Then, instead of the usually unnoticeable, brief hyperpnea, there will occur a violent reaction of the bronchi leading to an asthmatic attack. It is the cardiorespiratory disturbance, in such a case, that releases the attack of bronchial asthma. From this it is evident that the differentiation between cardiac and bronchial asthma, generally necessary and usually possible, cannot be made in every case.

In a further group of tuberculo-allergic asthma cases, the patients frequently complained of cardiac sensations—such as pressure and sharp pain in the sternal region—and also of spasms and precordial angina. These symptoms, which have often been falsely designated as cardiac neurosis, are usually produced by pleural adhesions (of the left mediastinal and basal pleura) leading to localized and pericardial adhesions.

Finally, we draw attention to the fact that in

²³VOIT, K., and LANDES, G. • *Klin. Wchnschr.* 17: 733 1938

cases of asthma of exclusively cardiac origin cautious therapy directed against the spasm of the bronchial musculature will give good results thus the conclusion might seem plausible that any paroxysmal dyspnea is associated with a bronchospastic component

11 ASTHMA AND PULMONARY TUBERCULOSIS

In the section on factors predisposing to asthma we have pointed out that its relation to pulmonary tuberculosis is still a disputed

In our own ¹⁰ material pulmonary tuberculosis plays a relatively minor role in the causation of or predisposition to asthma. As a rule only those forms of tuberculosis that present a high degree of allergy such as the hematogenous fibroproductive processes will lead to the development of a tuberculo allergic asthma. Thus in 412 cases of asthma pulmonary tuberculosis could be demonstrated as the major cause in only 25 cases or 5.5 per cent. The diagnosis of tuberculosis was based on the



FIG. 282 TUBERCULO ALLERGIC ASTHMA IN PATIENT WITH OLD FIBROUS TUBERCULOSIS OF LUNG
(Courtesy Dr. I. Solis Cohen)

question. Investigators who assume that there is an intimate interplay between the two are challenged by other experts who deny such a relationship and who attribute the simultaneous occurrence of the two diseases to the fact that both asthma and tuberculosis are relatively common diseases. Finally others believe that asthma and tuberculosis are mutually exclusive. Here we are concerned with some of the important clinical features that may be present when the asthma is of the tuberculo allergic type.

history and the clinical and roentgenologic evidence (FIG. 282) but special importance was attached to the results of the tuberculin tests. All of these 25 patients presented marked and prolonged local cutaneous reactions to old tuberculin persisting several days. In addition to the marked local reactions dilutions of from 1:10,000,000 to 1:1,000,000,000 actually elicited asthmatic attacks in 14 cases. In about half of these patients the asthma had already become pathergic i.e. there had originally been a

specific tuberculo-allergic asthma, but in the course of time the bronchial mucosa had become hypersensitive to various nonspecific agents (pathergens).

Among these cases there occurs a type of asthma characterized by certain clinical and hitherto unappreciated mechanical factors, and developing on the basis of a tuberculous infection. These cases are distinguished by the fact that the patients are not free of symptoms in the intervals between attacks, in that they have aches and sharp pain in the chest, incited or aggravated by changes in position, and exacerbated on deep respiration. Various bodily exertions cause pains in the sides or a sense of oppression. In addition, these patients often complain of substernal pain and pressure, as well as of spasms of precordial angina.

These "cardioneurotic" complaints are usual in certain forms of tuberculosis in which pleural adhesions, especially of the left mediastinal and the basal pleura, exert traction on the pericardium. The combination of such cardiac symptoms with bronchial asthma confirms the assumption that these asthmatics have the pleuropulmonary lesions already mentioned. In fact, in these cases we are repeatedly able to demonstrate, clinically and roentgenologically, the signs of bronchial lymph node disease with pleural involvement that Neumann²⁹ saw in benign hematogenous pulmonary tuberculosis. It must be mentioned, however, that the detection of such pleural changes by physical examination may often be difficult, because they usually involve only small portions of the pleural surface, and moreover are obscured by the gross noncharacteristic bronchitic râles of the asthmatic patient. This is especially true in regard to changes in the mediastinal pleura. Here the roentgenogram is also of little assistance unless gross lesions, such as displacement of the trachea (Fig. 283) or mediastinum, or pleural calcifications, are visible. On the other hand, great significance is attached to pleural changes such as apical induration or basal adhesions, which are clearly demonstrable roentgenographically. These changes may affect not only the general pleural surface, but the me-

diastinal pleura as well. A case may be cited to illustrate the pertinent points here discussed

M B, a white woman, 23 years of age, had pneumonia at the age of 8 and later "apical infiltration of the left lung." At the age of 19, she had costal pleurisy with thickening on the left side. After this illness she had dyspnea following even slight exertion, and two years later her first asthmatic symptoms occurred. From that time on she suffered from sudden attacks of palpitation that were severe even when she was at rest, so that she was totally incapacitated. Frequently these symptoms were followed by typical asthmatic attacks. Examination revealed a slender, somewhat anemic patient. Her lungs showed bilateral apical dulness of moderate degree. In the left paravertebral region the percussion note was impaired from the third to the seventh dorsal vertebra. Auscultation revealed bilateral occasional moist râles, as well as inspiratory crepitant râles in the region of the left paravertebral dulness. The roentgenogram showed a delicate pleural haziness in the right apex and the adjoining infraclavicular region. The left costophrenic angle was obliterated. Some months later, following moderately rapid ascent of a steep staircase, she developed severe dyspnea and marked palpitation, with a pulse rate of 150. Auscultation revealed a pleuropulmonary friction over the sternum. Four days later she gave a violent local reaction to 0.1 cc of 1:1,000,000 old tuberculin administered intracutaneously; and simultaneously complained of severe palpitation.

Thus we had a patient who suffered asthmatic attacks and in whom unequivocal tuberculous involvement of the mediastinal pleura could be demonstrated clinically. A characteristic feature was the association of severe cardiac symptoms with the dyspnea.

It appears that mechanical factors, such as enlarged tracheobronchial lymph nodes and, in particular, adhesive pleuritic processes, play some part in the release of asthmatic conditions in such cases. This is not meant to indicate that attacks of this sort depend entirely upon mechanically conditioned reflexes. Thus, if pleural changes develop many years after the onset of the asthma, obviously the latter cannot be blamed on the former, and these cases therefore cannot be included in the tuberculo-allergic group.

Other characteristic features of tuberculo-allergic asthma include constant subfebrile temperatures and the fact that during the relatively asymptomatic period the patients appear exhausted and fatigued, and show a tendency to perspire.

²⁹ NEUMANN, W.: Wien klin Wchnschr. 53: 1924, 1910.

In this connection we would also draw attention to an observation often made in cases with a diagnosis of tuberculo allergic asthma. Many of the patients had their attacks only when the supine position and could avoid nocturnal seizures by spending the night in a

sistent activity of the infection is a violent local reaction following the tuberculin test even with dilutions of 1:10,000,000 or 1:1,000,000,000.

Apart from 3 cases that were classified as advanced with cavitation all our other pa-



FIG. 283. ASTHMATOID SYNDROME PRODUCED BY HEALED TUBERCULOSIS

Considerable fibrosis of left upper lobe of lung caused deviation of trachea (arrow) which is response to for asthmato id symptoms

chair. In all these cases roentgenologic examination revealed enlarged hilar glands and in all there was a marked cutaneous hypersensitiveness to tuberculin.

An important evidence of tuberculous etiology is an accelerated blood sedimentation rate since this is normal or even retarded in other asthmatics. Another sign of the per-

tients belonged in the group of cases of fibro-productive tuberculosis. The advanced cases are nearly all tuberculo anergic, i.e. the skin is not capable of producing antibodies to the tubercle bacillus. The conclusion appears plausible that other organ systems as well such as the lungs may be incapable of an allergic reactive response. The mild hematogenous

forms of tuberculosis are usually marked by hypersensitiveness to tuberculin, so that in these cases the conditions for the development of allergic manifestations, provided the requisite predisposing factors are present, are considerably more favorable.

While, therefore, generally only the hematogenous forms of tuberculosis lead to asthma, there appear from time to time cases in which the asthma has been preceded by a fibro-ulcerative tuberculosis. Along with W. Neumann, we may explain this by the fact that in some instances cavernous pulmonary tuberculosis develops from dense fibrous tuberculosis and that only under such circumstances will a cavernous form show a high tuberculin allergy.

H G., a white man, 42 years of age, suffered an attack of hemoptysis fifteen years before admission to the hospital. At that time, early tuberculosis was diagnosed. Hemoptysis recurred four times in a period of three years. Examination of the lungs revealed, in addition to markedly impaired resonance at both apices, dullness at the left apex posteriorly above the level of the sixth dorsal vertebra, and bronchovesicular breath sounds in the same area. Over a limited region of the supraspinous fossa there were medium metallic râles. Subsequent roentgenologic examination revealed numerous small, closely approximated calcified foci in both upper lobes, and a cavitation of the size of a bean on the left. This was therefore a case of old tuberculosis (so-called tuberculosis fibrosa densa), with the development of a recent cavity. A violent local reaction followed injection of 0.1 cc. of 1:10,000,000 old tuberculin. While at rest at home, the patient suffered his first asthmatic symptoms, fourteen days after the last episode of hemoptysis. These persisted for about a week, with temporary relief by use of epinephrine.

This case shows clearly that a cavernous form may develop from a relatively benign tuberculosis, and asthmatic symptoms may appear for the first time during this stage of endogenous reinfection from a tuberculous process of at least fifteen years' duration.

In conclusion, it may be reiterated that only those forms of tuberculosis that have a high degree of tuberculin allergy are apt to develop asthma, and such cases are usually of the fibroproductive type.

One-fourth of all cases of tuberculo-allergic asthma are associated with cardiopathy, as pointed out in the section on asthma and cardiopathy.

In the treatment of tuberculo-allergic asthma, it is first necessary to determine

whether the case is still monospecific or whether it has already become pathergic, as had occurred in about one-half of our material. The authors have observed beneficial results from extremely cautious but prolonged intracutaneous tuberculin therapy. For the technic, see the section on therapy.

12. ASTHMA AND SKIN DISEASES

The question as to the relationship between skin diseases and asthma is of considerable interest. While neurodermatitis and its equivalent in childhood, infantile dermatitis, are the most important forms from the viewpoint of severity and difficulty of treatment, the urticarial group (urticaria itself, as well as lichen urticatus) are numerically of nearly equal consequence. Thus, it is worthy of note that among 452 cases studied by the senior author,²⁵¹ 38 patients, some of whom later developed neurodermatitis, had suffered from infantile dermatitis early in childhood, generally one or two years before the asthmatic symptoms began. Five per cent of the asthma patients had histories of disseminated neurodermatitis, and almost 12 per cent, of urticaria or related conditions.

Other authors arrived at even higher figures. Among 124 asthmatics, Baagoe²⁵⁰ found that 29 per cent had had neurodermatitis in childhood or in adult life, 27 per cent urticaria, and 11 per cent pruritus. According to Woringer,²⁵¹ about one-third of the asthmatic children in his extensive material had had neurodermatitis, while from 15 to 20 per cent of the entire infantile dermatitis group developed asthma in later childhood. Rost²⁵² reported similar findings: of 87 adult neurodermatitis cases, 23 (26.4 per cent) had asthma. Among 56 asthmatic patients observed by Casper,²⁵³ 25 simultaneously had dermatitis, while of 112 with eczematoid dermatitis, 10 had asthma. He also described 24 patients with chronic bronchitis and dermatitis. He believes that asthma and dermatitis are both expressions of the same constitutional diathesis.

It must be stressed, however, that, in the

²⁵⁰ BAAGOE, K. H. *Acta med. Scandinav.* 47: 149, 1927.

²⁵¹ WORINGER, P. *Bull. Soc. de pédiat. de Paris* 36: 406, 1939.

²⁵² ROST, G. *Arch. f. Dermat. u. Syph.* 135: 297, 1928.

²⁵³ CASPER, F. J. *Arch. Kinderh.* 115: 95, 1938.

vast majority of cases the associated skin diseases were due to allergens other than those causing the asthma. Above all, the pathogenesis of neurodermatitis is quite varied, hence the reader is referred to the discussion of this subject on page 713. The urticarial dermatoses are often attributable to hypersensitiveness to some food, occasionally to a drug. It is true, of course, that urticaria and asthma are sometimes elicited by the same excitant—e.g., ingestion of eggs, or the proximity of a rabbit. Occasionally, a patient may react with urticaria instead of the asthmatic response. This clinical observation led to the assumption that asthma is, indeed, a sort of urticaria of the bronchial mucosa (Talbot). The urticarial manifestations need not necessarily progress to the point of wheal formation, frequently, the only symptom may be an annoying or distressing pruritus.

This kind of itching is not to be confused with the pruritus to which Balyeat²²⁴ first called attention, and which he encountered in 13 among 420 asthma cases. The latter condition is confined to the upper portion of the thorax, as well as to the inter- and supra-scapular regions. Balyeat assumed it to be an expression of a viscerosensory reflex, arising from irritation of the bronchial mucosa and involving the fourth and fifth cervical nerves posteriorly, and the third cervical nerve anteriorly.

Aside from these localized forms, one occasionally encounters generalized pruritic paroxysms that may sometimes replace the asthmatic attack—that is to say, they act as asthmatic equivalents.

13 ASTHMA AND MIGRAINE

It would seem to be more than a mere coincidence that migraine is so frequently mentioned in the personal and family histories of asthma patients. Migraine was found in 13 per cent of women and 3 per cent of men with asthma. In the family histories, migraine occurred in 23 per cent of the ascendants of the female and in 13 per cent of those of the male patients, whereas all the other allergic diseases in our material²²⁵ do not exceed 4 or 5 per cent for each disease for all the members of the family. The predominance of the

female sex can be seen from the fact that about 70 per cent of the migrainous relatives were female, the great majority being the patients' mothers. These figures indicate that there is a close relationship between asthma and migraine. And this is further stressed by the fact that, in many patients, migraine and asthma appear alternately. In this connection, it is worthy of note what we found the same high incidence of migraine in the ascendants and siblings of urticaria patients—and here, too, far more frequently in the female sex.

14 DIAGNOSIS

The diagnosis of asthma is a relatively easy matter *during the attack*, since there are a number of symptoms and signs that are more or less characteristic of this condition. They include the labored respiration, with audible wheezing, the difficult and prolonged expiration, and the patient's posture (leaning forward, with the shoulders elevated). The percussion note over the lungs is hyperresonant. The inferior borders of the lungs are generally found to be from one to two interspaces lower than normal, as a result of acute emphysema. On auscultation, sibilant and sonorous rhonchi are heard over most of the lungs, especially during the prolonged expiratory phase, these completely obscure the underlying breath sounds. In some areas, where the bronchi have been almost completely occluded, one hears no breath sounds or only a faint wheezing on expiration. Aside from this, the findings are always present everywhere over the lungs and localization of the signs to restricted areas casts grave doubt on the diagnosis. The simultaneous presence of crepitant or subcrepitant râles should direct suspicion to some other condition or to some complication of asthma. A peculiar bubbling or rumbling type of rhonchus, especially over one or both lower lobes, is suggestive of bronchiectasis. According to Osgood,²²⁶ blood pressure readings during asthmatic paroxysms show marked fluctuations in the systolic phase, synchronous with the respiratory cycle and paralleling in degree the severity of the attack. The high point of the fluctuation always occurs in the expiratory phase, and the

low point during inspiration. Changes in the diastolic pressure are negligible. Fluoroscopic examination of the patient during an attack reveals depression and restricted mobility of the diaphragm.

During the symptom-free intervals, the establishment of the diagnosis is relatively difficult. At these times, one must depend principally on the history of paroxysms of dyspnea or of wheezing respiration, chiefly at night, with prompt relief from epinephrine or ephedrine. Furthermore, the personal history with regard to other allergic diseases, particularly hay fever, rhinopathy, neurodermatitis, and urticaria is often helpful. The family history is also worthy of close attention in this respect.

Clinical investigation of a case of asthma should include the following studies (some of which may be omitted in clear-cut exogenous-allergic cases): urinalysis, complete blood count, nasal smears for cytology and bacteria, sputum examination for eosinophils and tubercle bacilli, roentgenograms of the sinuses and chest with fluoroscopic examination of the chest or X-ray films taken at the height of inspiration and expiration, serologic test for syphilis, blood sedimentation rate, and vital capacity; and, in selected cases, circulation times, venous pressure, sputum culture, bronchoscopy, and bronchograms.

VITAL CAPACITY

The vital capacity—that is, the entire range between maximal inspiration and maximal expiration, which normally amounts to about 3,500 to 4,000 cc.—is greatly reduced (to about 40 per cent of normal) in severe asthma and moderately (to about 60 per cent) in milder cases, according to Feinberg's²⁵⁶ investigations. Wittich et al.²⁵⁷ had previously demonstrated the marked diminution in vital capacity in asthma in comparison with other pulmonary diseases. The decrease in vital capacity is due to the great increase in the residual air or so-called dead space of the lungs (Fig. 284).

Even during symptom-free intervals, the vital capacity is by no means normal, but

only about 80 per cent or less, as the result of emphysema, chronic bronchitis, or bronchiectasis. Repeated determination of the vital capacity is valuable in following the degree of improvement resulting from the therapeutic measures employed. This test also has prognostic significance since a reduction of 50 per cent or more in the vital capacity of a patient not in an acute asthmatic attack and at rest, makes it exceedingly unlikely that any great benefit will ensue from any type of therapy.

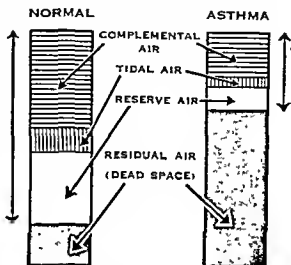


FIG. 284 COMPARISON OF RESPIRATORY CAPACITY UNDER NORMAL CONDITIONS AND IN ASTHMA

Note differences in residual air (dead space) and in vital capacity (extent of maximum respiratory movement), the latter being indicated by the double-headed arrows

A simple, clinically useful set of normal standards for vital capacity was proposed by Peabody and Wentworth^{257a}:

Height	Men	Normal Vital Capacity
Over 72 inches		5,100 cc
68½ to 72 inches		4,800 cc
63 to 68½ inches		4,000 cc
	Women	
Over 66 inches		3,275 cc
64 to 66 inches		3,050 cc.
61 to 64 inches		2,825 cc.

More complete standards for estimating the deviation from the normal values based on body surface area (as determined from sex, age, height, and weight), were prepared by

²⁵⁶ FEINBERG, S. M.; *J. Allergy* 1: 506, 1930

²⁵⁷ WITTICH, F. W., MYERS, J. A., and JENNINGS, F. L.; *J. A. M. A.* 75: 1249, 1920.

^{257a} PEABODY, F., and WENTWORTH, J.; *Arch. Int. Med.* 20: 443, 1917

Edwards and Wilson^{2,58} However in following the clinical course or results of therapy by serial determinations in the same patient no such comparisons are necessary.

Since the results of a properly performed breath holding test bears a fairly constant relationship to the vital capacity (Wittich and Polczak^{2,58}) it may usefully be substituted for the latter when facilities are not available.

SPUTUM

In paroxysms of short duration there may be no sputum at all. But as a rule and particularly toward the end of the attack the patient coughs up a scant viscid secretion grayish white and mucoid in appearance.



FIG 285 CHARCOT LEYDEN CRYSTALS IN SPUTUM

This contains in addition to the usual ingredients of the ordinary bronchitic sputum varying amounts of yellowish or sometimes grayish flakes. The yellowish ones are usually extremely viscous and consist of bloated and fatty degenerated leucocytes and ciliated epithelial cells among which one frequently sees large numbers of sharp edged crystals the Charcot Leyden crystals (FIG 285). When the attack subsides the number of these crystals in the sputum usually drops rapidly. Nothing whatever is known about the reasons for the formation of these crystals. Probably their appearance is somehow related to the presence of eosinophile cells in the sputum. In any event the crystals always seem to be encountered wherever disintegrating eosinophile cells are present.

The grayish plugs in the secretions of asthma patients consist principally of tangled thread of mucus and contain strange spirals

first described by Curschmann and now generally known as Curschmann spirals (FIG 286). Many of these formations are actually recognizable with the naked eye as consisting of a spiral of twisted threads of the thickness of a needle and from 0.5 to 2 cm in length others however cannot be seen without a microscope under which they present a light shiny formation composed of many fine and coarser little bands and threads twisted together in a sort of spiral. In the middle there is usually a fine brightly shining central thread. Around the spirals one finds lymphocytes fat and myelin droplets and occasionally also ciliated and alveolar epithelial cells. Nothing as yet is definitely known concerning the manner in which the spirals and the central threads are formed it is clear however that they represent casts of the finest bronchioles twisted into spirals. The origin of the central thread probably depends on compression of the mucus by contractions of the bronchi during coughing spells these cause the central portion of the ropelike twisted mucus to become so dense that it appears as a gleaming homogeneous thread.

Among other peculiarities of the sputum in bronchial asthma special mention should again be made of the almost invariable presence of strikingly numerous eosinophile cells. These are recognizable in unstained preparations by the strange radiance of the granulations. Crystals spirals and eosinophile cells are best seen in sputum taken at the end of the attack. Among the occasional findings in the sputum of asthmatics one might mention crystals of calcium oxalate and calcium phosphate.

Fuchs Spain and Strauss⁵⁹ found that the cholesterol content of the sputum in asthma ranges from 7 to 55 mg per cent and was high (25 to 55 mg per cent) in the infective or skin negative types. The amount varied with the severity of the clinical symptoms and it is suggested that repeated analyses of the sputums for cholesterol may be helpful in conjunction with other findings in evaluating the patient's course. Moreover since high values were not obtained from the skin sensitive group in which the specific causes are

² EDWARDS D. J. and WILSON M. G. J. Lab. & Clin. Med. 24: 543, 1939.

⁵⁸ WITTICH F. W. and POLCZAK J. A. Am. Rev. Tuberc. 13: 54, 1926.

⁵⁹ FUCHS A. B. SPAIN W. C. and STRAUSS M. B. J. Allergy 14: 236, 1944.

pollens, inhalants, and foods, this test may be of value in differentiating this type from those whose symptoms are caused or aggravated by infection of the bronchi and paranasal sinuses.

When a bronchial infection is present, the sputum first becomes mucopurulent and then yellowish or greenish. Many organisms, particularly hemolytic and nonhemolytic streptococci, *Staphylococcus aureus*, pneumococcus, Friedlaender's bacillus, *Micrococcus catarrhalis*, and yeast will be found in varying proportions and amounts

hypersensitiveness to a protein (e.g., to cat hair) cannot be differentiated by this means from bacterial asthma, for example. The rest of the blood picture is also not diagnostic.

The sedimentation rate is usually normal or slightly decreased. However, in cases of the infectious type, the rate may be markedly increased. At the same time, it must be said that extensive investigations carried out by various authors, including the senior author (on 158 cases), did not give results uniform enough to permit this approach to be used for

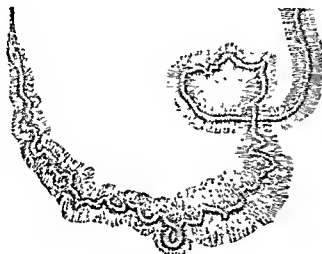


FIG. 286. MICROSCOPIC APPEARANCE OF CURSCHMANN SPIRAL

BLOOD

A rather marked eosinophilia (10 to 30 per cent) is often found in the blood, especially when the attack is subsiding; but a moderate degree of eosinophilia, usually associated with lymphocytosis, is also present sometimes in the symptom-free intervals. At the beginning of the attack, there is an increase in the neutrophilic polymorphonuclear cells, while the number of eosinophils decreases sharply; this, however, rises abruptly toward the end of the attack.

On the other hand, eosinophilia may be completely lacking or may be of only slight proportions. Moreover, its degree is in no way related to or indicative of the severity of the disease or of the nature of the eliciting factor. In other words, cases attributable to

differentiating between the different types of asthma

The Weltmann reaction, based on the coagulation of the patient's serum by serial dilution of calcium chloride from 0.1 to 0.01 per cent, can be more successfully used for this purpose, according to Dees.²⁸⁰ Patients with uncomplicated asthma, or asthma and another allergic disease, have normal coagulation bands of 6, while those with noninfectious complications, including fibrotic and degenerative processes, have bands of 7 or longer. Asthmatics with infections have bands less than 6, except when pulmonary fibrosis coexists, in which case the result is determined by the balance between the two processes.

²⁸⁰ DEES, S. C. *J. Allergy* 14: 469, 1943

ROENTGENOLOGIC EXAMINATION

The thorough diagnostic study of a case also requires roentgenologic examination of the lungs especially because of the difficulty of carrying out a careful physical examination in view of the frequent bronchitis and emphysema. Fluoroscopic and roentgenographic

infection (Fig. 288) and enlarged thymus in children (2) to exclude the possibility of congenital diseases including dextrocardia, bronchiectasis and tuberculosis (3) to disclose the presence of diseases resulting from asthma such as emphysema, atelectasis, subcutaneous emphysema, spontaneous pneumo-

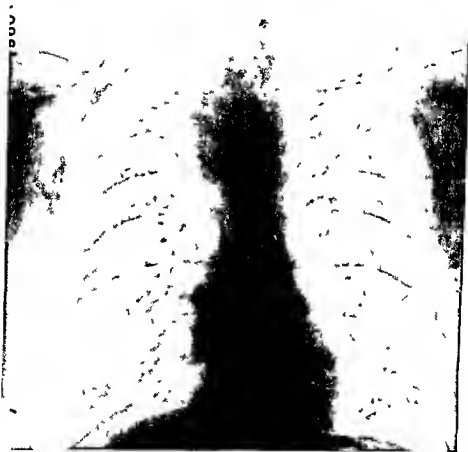


FIG. 287 BENIGN TUMOR OF ANTEROSUPERIOR MEDIASTINUM COMPRESSING TRACHEA AND PRODUCING ASTHMATOID SYMPTOMS

(Courtesy Dr. L. Solis Cohen)

study of the chest has four principal purposes (1) to rule out the possible presence of pathologic conditions that cause sufficient obstruction of the bronchi to produce dyspnea and wheezing such as foreign bodies, neoplasm (Fig. 287), aneurysm, substernal thyroid, tracheobronchial lymphadenopathy, pulmonary suppuration, tuberculosis, syphilis, mo-

thorax, spontaneous fractures of the ribs, and pneumonitis, and (4) to discover other forms of allergic manifestations in the lungs such as allergic pulmonary infiltrations and Loeffler's syndrome.

All of these diseases or symptoms are discussed in the appropriate sections of this chapter. Here we shall consider only the

roentgenologic findings in bronchial asthma itself. And, to begin with, it must be said that there is no roentgenologic picture that is really characteristic of this disease.

During the symptom-free intervals, one finds, especially in chronic asthma, the following X-ray changes—which, however, are also frequently observed in chronic bronchitis, as pointed out by Manges and Hawley,^{1,2} Zdansky, and Dillon and Gurewitsch: (1) enlargement and increased density of the hilar

tuberculosis; (2) depression of the diaphragm, with a definitely restricted respiratory mobility; (3) increased air content of the lungs, with widening of the intercostal spaces; (4) pleural changes such as diaphragmatic and pleuro-pericardial adhesions and interlobar or paramediastinal pleuritides; (5) enlargement of the bronchial lymph nodes; (6) minute round dense shadows resulting from bronchiolitis; (7) shadows of various sizes with a peribronchial distribution, scattered throughout the lungs,



FIG. 288 YEAST INFECTION OF LUNGS SIMULATING BRONCHIAL ASTHMA

(Courtesy Dr. L. Solis-Cohen)

shadows with coarse streaks radiating from these and representing the thickened bronchi, extending down into the lower lobes, and rarely into the other parts of the lung fields, in the hilar shadow itself and in its immediate proximity, the occurrence of thickened bronchi in cross section, producing annular shadows of irregular contour; the apices are normal in appearance except when there is coexistent

but chiefly at the bases, these are the result of the viscid secretions due to severe bronchitis; (8) bronchiectasis, which often can be detected only by intratracheal instillation of radiopaque oil.

However, it must be stressed that at least 16 per cent of all cases of asthma present normal X-ray findings in the lungs (Manges and Hawley²⁻⁴).

In contrast with ordinary roentgenograms, bronchographic study of 52 cases of bronchial

^{1, 2} MANGES W. F., and HAWLEY, S. J. *South M J* 20: 126, 1927

asthma by Truog²⁹⁶ indicated that there is a definite roentgenologic picture in this disease when this technic is employed. It consists essentially of the demonstration of a partial or complete occlusion of many of the bronchi. Narrowing occurred as an early change and was present in patients with less severe attacks (63 per cent). Occlusion was demonstrated in 83 per cent as a convex distal border of the column of the radio opaque oil, giving a characteristic "snub nosed" appearance, although some had straight margins. Both narrowing and occlusion often occur together (48 per cent). A cylindrical dilatation of the bronchi with fairly marked degree of occlusion was noted in patients with severe attacks. The close correspondence of these findings with the pathologic lesions described above is apparent. However, bronchography during attacks of asthma for the confirmation of the diagnosis is not recommended.

According to Mansmann and Osmond,^{2198a} indirect evidence of these processes, particularly bronchial occlusion, may be adduced by chest films taken at the height of inspiration and expiration, by fluoroscopic examination, and/or by a single double exposure inspiratory expiratory film. The roentgenologic findings demonstrable by such technics are dependent upon the impediment to the movement of air into and from the segment of pulmonary tissue beyond the region of the stenosis, and upon the retention of bronchial secretions. They include an inspiratory shift of the heart to the affected side, usually a thickened fuzzy outline of bronchovascular markings in the region, frequently with a superimposed fan-like area of slightly or considerably increased density, and, if atelectasis is present, decreased range of motion of the diaphragm on the affected side with a higher dome on full inspiration.

On the other hand, a comparison of the usual roentgenogram taken during an acute attack, as well as in status asthmaticus, with that taken during the interval, reveals only minor changes. There is not even an appreciable change in the position of the diaphragm, this may be explained, however, by the fact that in many cases the diaphragm is already

so depressed that the increased pulmonary volume during the attacks is achieved only by elevating the ribs. The lung fields themselves are also generally changed to only a very slight extent during an attack. In relatively rare instances, the markings that are ordinarily increased in most cases of asthma, are intensified in long lasting attacks. Such an increase is more often observed in patients with abundant secretion and expectoration, owing to the filling of the larger lower bronchial branches with exudate.

Kornblum²²⁶³ reported roentgenologic findings in the acute attack that resemble pneumonic conditions, but that disappear when the attack subsides or on administration of epinephrine.

On fluoroscopy, it will be seen that the heart of the small narrow vertical type ('drop heart'), as shown in FIGURE 273. This is probably due to the emphysema and the consequent flattening of the diaphragm, which pulls the organ down and rotates it slightly medially. Furthermore, Moritz noted the interesting finding, during the asthma attack, of an increase in the size of the heart during inspiration and a decrease during expiration—representing the reverse of the normal relationship. It is also frequently seen in the interval between attacks.

The roentgenogram in asthmatic infants is similar to that of adults, and is characterized by the lowered diaphragm with limited excursions, by the horizontal position of the ribs, with widened interspaces, the vertically elongated hilar shadow, the increased parenchymal transparency, and by certain daubed appearing shadows in the parenchyma, suggesting a bronchoalveolar exudate (Debre and associates²²⁶⁴).

BRONCHOSCOPIC EXAMINATION

Bronchoscopy offers additional aid in diagnosis. The use of this method is indicated (1) in any case of asthma presenting physical signs of bronchial obstruction due, for example, to bronchial stenosis, foreign body, or neoplasm, (2) to determine the presence of complicating secondary bronchial infection,

²²⁶³ KORNBLUM K. *Laryngoscope* 52: 128, 1942.

²²⁶⁴ DEBRE R, LAMY M, MIGONV M and NICK J. *Presse méd* 47: 957, 1939.

particularly suppurative tracheobronchitis, bronchiectasis, and pulmonary abscess; (3) for the collection of specimens of uncontaminated bronchial secretions for cytologic and bacteriologic studies; and (4) before bronchography, and for the instillation of lipiodol for a bronchogram, although other methods may be used for the last. Certainly, endoscopic investigation is warranted in any case of atypical asthma which does not respond readily to diagnosis and therapy (Friedberg²⁸⁵).

The bronchial mucosa examined in the symptom-free interval between attacks may have a fairly normal appearance, or may be inflamed and velvety if tracheobronchitis is present. During an attack, the lining mucosa will be found to be swollen, edematous, and

aspects of the differential diagnosis of bronchial asthma.

It would lead us too far afield if we undertook anything like a detailed discussion, from the viewpoint of differential diagnosis, of all the conditions mentioned in the table. We shall be obliged to confine our remarks to the most commonly encountered and most important asthmatic conditions. In cases in which clinical examination fails to reveal any kind of organic disease, pneumograms may be of great help. This procedure, presenting a curve of the patient's respiration, permits analysis of the course of the respiratory movements, and discloses any hindrance, also the degree and the time of interference with breathing—i.e. whether only during inspira-



FIG 289 PNEUMOGRAPHIC CURVE OF NORMAL SUBJECT

E = expiration I = inspiration

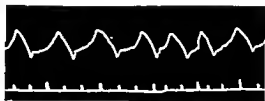


FIG 290 PNEUMOGRAPHIC CURVE DURING ATTACK OF BRONCHIAL ASTHMA

purplish, and the bronchi to be filled with a thick viscid secretion (Prickman and Vinson²⁸⁶). Furthermore, there is an accentuation of the physiologic postero-anterior narrowing that occurs in the trachea and the larger bronchi during expiration, sometimes leaving nothing more than a slitlike opening of the lumen of these passages. This is probably due to the increased intrathoracic pressure exerted on the weak posterior wall.

15. DIFFERENTIAL DIAGNOSIS

Before making a diagnosis of asthma, the physician should always keep in mind that "all is not asthma that wheezes" (Chevalier Jackson).

Maytum²⁸⁷ has given a complete classification of the conditions that may cause dyspnea and that may be mistaken for asthma (Table 54). Sodeman²⁸⁸ has recently reviewed some

tion or expiration, or during the entire respiratory cycle (Hofbauer²⁴⁹). FIGURE 289 shows the graph of a normal individual and FIGURE 290 that of a patient in an acute bronchial asthmatic attack.

a) CARDIAC CONDITIONS SIMULATING ASTHMA

The term *cardiac asthma* is used to designate the severe attacks of dyspnea that occur in patients with cardiac disease when there is inequality between the output of the right and of the left heart, usually owing to a sudden relative failure of the left ventricle while the right ventricle continues to function normally. This occurs chiefly in hypertensive and syphilitic heart disease, syphilitic aortitis, and rheumatic heart disease of long standing. As a result of the impairment of cardiac function, there is pulmonary congestion, leading ultimately to pulmonary edema. This disturbance causes dyspnea, cough (at first a dry irritative cough), expectoration, and cyanosis. The increased pressure in the pulmonary cir-

²⁸⁵ FRIEDBERG, S. A. J. A. M. 123: 85, 1943

²⁸⁶ PRICKMAN, L. E., and VINSON, P. P. J. Allergy 4: 256, 1933

²⁸⁷ MAYTUM, C. K. M. Clin. North America 14: 529, 1939

²⁸⁸ SODEMAN, W. A. Am. J. M. Sc. 210: 114, 1945

TABLE 54—*Classification of Conditions That May Cause Dyspnea and May Be Mistaken for Asthma (Continued)*

I RESPIRATORY SYSTEM			
A Larynx	B Trachea and bronchi	C Lung	
1 Laryngeal spasm	1 Intrinsic lesions	1 Inflammation	
a) spasmodic croup	a) acute and chronic bronchitis	a) pneumonia	
b) laryngismus stridulus	b) chronic inflammation with stenosis	b) tuberculosis	
c) laryngeal crisis of tabes dorsalis	bronchiectasis	c) pneumoconiosis and pulmonary fibrosis	
2 Inflammation	tuberculosis	2 Idiopathic pulmonary emphysema	
a) acute	siphilis	3 Neoplasm of lung and pleura	
acute laryngitis	foreign body	4 External pressure	
diphtheritic laryngitis	c) neoplasm	a) pneumothorax	
chronic	benign	b) hydrothorax	
tuberculosis	malignant		
siphilis	2 Extrinsic lesions		
3 Angioneurotic edema	a) substernal enlargement or carcinoma of thyroid gland		
4 Paralysis of vocal cords	b) enlargement of thymus gland		
5 Laryngeal stenosis	c) aneurysm of thoracic aorta		
6 Foreign body	d) tuberculous tracheobronchial nodes		
7 Neoplasm	e) mediastinal neoplasm		
a) benign	benign		
b) malignant	malignant		
II CIRCULATORY SYSTEM		III RENAL SYSTEM	
A Cardiac decompensation	Dyspnea due to myocardial degeneration	IV NERVOUS SYSTEM	
B Coronary sclerosis		A Functional air hunger	
C Paroxysmal auricular flutter or fibrillation		B Hyposternal polypnea	
D Paroxysmal tachycardia		C Respiratory syndrome following encephalitis	

culation is usually expressed by an accentuation of the second pulmonic heart sound, signs of hypertension in the lesser circulation, enlargement of the left ventricle, and, in most cases, murmurs. Although it is true that cardiac asthma generally affects individuals who are known to be suffering from some heart condition, others, who have previously felt perfectly well, can also be attacked in this manner, without any warning. If interrogation reveals that the patient has previously had no complaints referable to the heart, and if examination during the attack discloses no distinct evidence of cardiac damage, an erroneous diagnosis of bronchial asthma is often made during the first seizure, especially in the case of young individuals. Moreover, the dyspnea is generally of a distinctly expiratory type, and the physical findings in the lungs are generally the same as those in bronchial



FIG. 291. PNEUMOGRAPHIC CURVE IN CARDIAC ASTHMA

asthma, although they may be accompanied by the presence of crepitant râles at the bases. Lastly, according to Scherf and Boyd²¹⁴ blood eosinophilia may appear in the intervals between attacks.

The three following symptoms are fairly characteristic of cardiac asthma: the sudden onset, usually at night, the shortness of breath, combined with fear; and, usually, the complete absence of pain. Epinephrine does not, as a rule, control the dyspnea as promptly in this condition as it does in bronchial asthma, appropriate cardiac therapy, on the other hand, is effective.

As mentioned elsewhere (p. 605), circulation time tests are exceedingly valuable in distinguishing the two forms. Venous pressure determinations are also useful. In addition, cardiac and bronchial asthma can be differentiated, according to Hofbauer,²¹⁵ by means of pneumographic examination. In the former condition, one invariably observes a regular prolongation as well as a relative flattening of inspiration and expiration; here the expiratory phase presents a steadily rising line (Fig. 291),

in contrast to the jerky line registered in bronchial asthma.

The differentiation between these two conditions is of great therapeutic importance, since morphine is the sovereign drug in the cardiac types, but is contra-indicated in bronchial asthma, while the opposite is true of epinephrine. However, not altogether rarely in asthma of long standing or in elderly patients, bronchial asthma and dyspnea due to heart disease may coexist.

The term *cerebral asthma* is used by Straub to designate paroxysmal nocturnal dyspnea in patients with hypertension but without renal insufficiency. In these patients there is a decided reduction of carbon dioxide tension and a shift of the blood reaction toward the alkaline side, owing to the marked hyperventilation. The latter is explained by asphyxia and local disturbances of circulation in the cerebral centers. The vascular changes are said to be due to organic changes or spasm. Since these attacks yield to digitalis therapy, Scherf and Boyd²¹⁴ hold that they belong to the group of cardiac asthma. But the latter term should not be applied to the dyspnea occurring in patients with cardiac decompensation, for it is neither paroxysmal nor accompanied by wheezing respiration. These conditions are, therefore, properly termed cardiac dyspnea.

b) PULMONARY CONDITIONS SIMULATING ASTHMA

Asthmatoïd Cough

As a result of irritation of the mucous membranes in various inflammatory diseases of the upper respiratory passages, and especially in tracheitis, attacks of coughing are produced that (when there is a delay in the elimination of the secretions) gradually increase in intensity and may ultimately assume the character of an asthma-like condition.

Asthmatoïd Bronchitis

Chronic infection of the bronchi may lead to an inflammatory swelling of the mucosa, as a result of which dyspnea and wheezing frequently appear. Moreover, in chronic bronchitis, especially in children and in the aged, the cough is also one of the most characteristic and distressing features. It is often paroxys-

mal in character, sometimes even resembling whooping cough. The sputum is always of the mucopurulent type, and is usually much more profuse than in the exogenous-allergic type of asthma. In asthmatoïd bronchitis, the râles and rhonchi are exclusively or pre-dominantly in the inspiratory phase of respiration. The question as to whether there is an infectious process that leads mechanically to a partial obstruction of the bronchial lumen or whether an infection is responsible for bacterial hypersensitiveness on the basis of which bronchial asthma develops, must be determined in each case. This bronchitis is, naturally, not to be confused with the acute form observed during or at the end of an attack of allergic asthma. When the asthmatoïd symptoms are due to mechanical interference, the dyspnea is continuous rather than paroxysmal and fails to respond satisfactorily to epinephrine. Exacerbations of chronic bronchitis or recurrent acute episodes may also give rise to infrequent but rather prolonged attacks of asthma-like symptoms. In children, on the other hand, the catarrhal factor sometimes dominates all the symptoms of spasm, as a result of this, the first asthmatic attacks are frequently not recognized as such, but are often diagnosed as recurrent bronchitis, until typical seizures occur. Repeated attacks of bronchitis in children with family histories or other evidences of hypersensitiveness, such as urticaria, dermatitis or migraine, strongly suggest, however, that the conditions in question are of allergic origin. In elderly individuals, the persistence of the cough for some time may be regarded as a sign that the condition is not fundamentally allergic. Brown¹⁶³⁵ has reviewed the symptomatology and findings of asthma due to bacterial allergy.

The differentiation between asthmatoïd bronchitis and true bronchial asthma due to bronchial infection and/or bacterial hypersensitiveness is often difficult and not always possible. However, a determined effort should be made to distinguish between these two conditions since, to a large extent, the nature of the treatment and the prognosis are determined thereby. The differences noted in Table 55 (in which data on exogenous allergic asthma are included for comparison) will usually make a precise diagnosis feasible. It

must be admitted, however, that certain border line cases share the characteristics of both conditions.

The sino bronchial syndrome in children has received careful attention from Dutton and Fuchlow.²⁷⁶⁹ It consists essentially of an asthmatic bronchitis in association with hy-perplastic sinusitis, and may appear as a complication of bronchial asthma. The condition is chronic with residual symptoms of mild character between acute attacks, which last from four days to two weeks and which are accompanied by fever, rhinitis, postnasal drainage, cough, and wheezing. X-ray treatment over sinuses and chest is said to give satisfactory results.

Asthmatoïd Emphysema

Quite frequently one sees patients with chronic emphysema and dyspnea erroneously diagnosed as bronchial asthma. Here too the attacks are not paroxysmal. The dyspnea may be explained by the marked reduction in functioning pulmonary tissue.

Mention should also be made of the dyspnea occurring in coal miners after many years of exposure to silica dust (so-called miner's asthma) and caused by pneumoconiosis.

c) INTRATHORACIC PROCESSES SIMULATING ASTHMA

Patients with pulmonary tuberculosis often present respiratory difficulties that are due to tuberculo-allergic asthma in only a small percentage of cases. In the others, they are produced by conditions resulting from the pulmonary tuberculosis such as displacement of the mediastinum, deviation of the trachea and of the main bronchi, and pleural adhesions. Furthermore, the tuberculous process can, through fibrosis and adhesions, place the heart and the circulation at a mechanical disadvantage.

On the other hand, as Fraenkel⁷⁷⁰ points out, an active and open tuberculosis can long be concealed under the guise of a bronchial asthma. This appears to be particularly true when there is tuberculous tracheobronchitis, as has been repeatedly demonstrated recently

²⁷⁶⁹ DUTTON L. O. and FUCHLOW J. R. *Ann. Allergy* 3: 447, 1945.

⁷⁷⁰ FRAENKEL E. M. *Brit. M. J.* 2: 513, 1934.

TABLE 55—*Differential Diagnosis of Exogenous-Allergic Asthma Infectious (Bronchitis) Asthma, and Asthmatoïd Bronchitis*

	Exogenous Allergic Asthma	Infectious Bronchitis Asthma	Asthmatoïd Bronchitis
Age of Onset	Any—uncommon in older individuals	Usually past middle age, but may occur in children	Children or adults
Family History of Allergy	Often positive	Variable	Rare
Symptoms	Expiratory dyspnea and wheezing, cough variable and usually late in attack	Expiratory dyspnea and wheezing, plus considerable cough	Cough predominates and initiates symptoms, "rattling" rather than wheezing, little or no real dyspnea
Fever	Rare	Often, low-grade	Usual, may be high
Onset of Attacks	Usually abrupt	Gradual	Usually very gradual, appearing as complication of existing bronchitis, no clearly defined paroxysms
Duration	Paroxysmal, usually brief	Variable, often low grade prolonged attacks with exacerbations	More or less continuous or may occur as infrequent prolonged episodes
Symptoms in Intervals	None	More or less persistent low-grade symptoms, exacerbated by upper respiratory infection, physical exertion, chilling, etc.	Cough and expectoration
Seasonal Incidence	Not seasonal (or corresponds to pollen seasons)	Perennial, worse in winter or with change of seasons, in damp or rainy weather	Occurs chiefly in winter or with change of seasons
Physical Signs	Typical acute pulmonary emphysema, expiratory rales, prolonged expiratory phase	Same, but not as marked, often numerous sibilant inspiratory rales	Predominantly inspiratory rhonchi, often very coarse, expiratory phase not prolonged
Sputum	Scant, mucoid, grayish white	Mucopurulent, quantity variable	Profuse, mucopurulent, greenish-yellow
Eosinophils in Sputum	Usual	None or occasional	None
Cholesterol Content of Sputum	Normal	Increased	Increased
Nasal Discharge (if present)	Thin, clear, watery, contains eosinophils	Purulent or mucopurulent, eosinophils variable	Thick, sticky, yellowish; no eosinophils
White Blood Cell Count	Leucocytosis infrequent	Normal, or mild leucocytosis	Frequent leucocytosis
Blood Sedimentation Rate	Normal or retarded	May be accelerated	Usually accelerated
Wetmann Reaction	Normal (band 6)	Bands less than 6 (unless pulmonary fibrosis exists)	Bands less than 6
Vital Capacity	Reduced during attacks and often between attacks	Same	Normal (except with emphysema)

TABLE 53—*Concluded*

	Exogenous Allergic Asthma	Infectious (Bronchitis) Asthma	Asthmatoid Bronchitis
Bacteriology	Indifferent	Usually Strep. Staph. or Pneumococcus	Same
X-ray of Chest	Normal or minimal changes	Exaggerated peribronchial markings, coalescence of hilar shadows	Same
Skin Tests	Positive reactions usually obtained	Usually positive reactions only to bacterial products esp. autogenous vaccines	Usually no positive reactions occasionally positive to bacteria or their products
Response to Epinephrine	Good	Relieves acute phase of symptoms	Poor
Response to Chemotherapy and Antibiotics	None	Limited response	Excellent
Complications (emphysema, bronchiectasis)	Rare	Frequent	Infrequent
Prognosis	Generally good	Usually poor as regards morbidity and disability	Generally good

(Menendez and Hernandez Gonzalo,²⁷⁷¹ Oatway, Gale, and Mowry,²¹⁴³ Waldbott²¹²⁵)

Other intrathoracic processes that may exert direct or indirect pressure on the bronchi, and thus simulate asthma, include aneurysm of the aorta (FIG 292), peribronchial and mediastinal lymphadenitis, bronchial, extra bronchial, and mediastinal tumors (FIG 287), diverticulum of the esophagus (FIG 293), sarcoidosis with bronchial involvement, substernal thyroid (FIG 294), and retropharyngeal abscess. Stridor is never the result of uncomplicated asthma. Its presence, therefore, should suggest some other condition. Recurring hemoptysis in an asthmatic, although it may be associated with a severe cough, points to the possibility of neoplasm or other organic pulmonary disease, as recently again emphasized by Prickman and his associates.²²⁷² However, pulmonary neoplasms can closely simulate asthma from the standpoint of both history and physical examination, whether bronchogenic carcinoma, as in 4 cases reported by Moore,²²⁷³ or generalized endolymphatic carcinomatosis (pulmonary metastases), as in 2 cases described by Men-

deleff.²²⁷⁴ Syphilis is rarely the cause of asthma, but should never be overlooked (Klinefelter²²⁷⁵). Lastly, mention is still to be made of the possible presence of foreign bodies in the respiratory passages, particularly in children.

The differential diagnosis of these processes is generally not too difficult. The possibility of bronchial asthma can generally be ruled out by painstaking clinical examination and X-ray and bronchoscopic findings in connection with a negative history as to allergy.

d) RESPIRATORY NEUROSES SIMULATING ASTHMA

Hysteric tachypnea may occasionally simulate asthma clinically. It is usually the expression of a reaction to some psychic trauma, such as fright, severe emotional upset, or very fatiguing exertion and occasionally also the direct result of witnessing an attack in another patient. The diagnosis can be made clinically on the basis of the absence of sputum, both during and after the attack, and also of the extraordinarily sudden onset and disappearance of the acute symptoms. Moll²²⁷⁶ suggested mecholyl as a help in establishing the differential diagnosis, while the

²⁷⁷¹ MENENDEZ F. J. and HERNANDEZ GONZALO P. D's Chest 8: 382, 1942.

²²⁷² PRICKMAN L. E., MAYTUM C. K. and MOERSCH H. J. J. Allergy 13: 261, 1942.

²²⁷³ MOORE M. W. Ann. Allergy 3: 271, 1945.

²²⁷⁴ MENDELEFF A. I. Ann. Int. Med. 22: 386, 1945.

²²⁷⁵ KLINEFELTER E. W. Arch. Dermat. & Syph. 37: 80, 1938.

subcutaneous injection of from 10 to 20 mg of this choline derivative elicits wheezing or even an acute attack in asthmatic individuals, it does not do so in cases of respiratory neurosis

which, according to Browning,²⁷⁶ is a rather suspicious sign. Sighing dyspnea is always a functional disorder due to an underlying neurogenic cause. However, it is impossible sometimes to distinguish sharply between an



FIG. 292. LARGE AORTIC ANEURYSM PRODUCING ASTHMATOID SYMPTOMS

(Courtesy Dr. L. Solis Cohen)

The syndrome of sighing dyspnea also merits discussion here. It consists of deep sighing respirations that are greatly increased in depth, without much alteration in the respiratory rate. If the attack is long and severe, tetany may occur from hyperventilation. The history is the most important means of making this diagnosis in the interval. When asked to imitate the symptoms, the patient will often take a deep sighing inspiration,

allergic asthma and a neurosis, since the latter can act as a predisposing factor in producing asthma (see p. 570).

Faulty diaphragmatic function, demonstrable fluoroscopically, can also be responsible for intense dyspnea which may be confused with asthma. According to Day,²⁷⁷ this syndrome of diaphragmatic dyspnea, occur-

²⁷⁶ BROWNING, W. H. *South. M. J.* 35: 914, 1942.

²⁷⁷ DAY, G. H. *J. Roy. Army M. Corps* 81: 290, 1943.



FIG 293 ESOPHAGEAL DIVERGENCE PRESSING ON TRACHEA THIS PRODUCES ASTHMATOID SYMPTOMS
(Courtesy Dr. L. Solis-Cohen)



FIG 294 SUBSTERNAL THYROID RESPONSIBLE FOR ASTHMA LIKE DYSPNOEA
(Courtesy Dr. L. Solis-Cohen)

ring under conditions of strenuous exertion, was the commonest disorder of the respiratory system in the British Army in World War II. The excursions of the diaphragm are found to be slight, absent, or paradoxical, and the treatment consists of controlled breathing exercises

16. ETIOLOGIC DIAGNOSIS

When the diagnosis of asthma has been established, the diagnostic difficulties really begin. The physician must now discover the

the case under consideration. It also includes a number of queries that should be put to the parents of asthmatic children; the answers are likely to be highly significant, since they give the physician a better understanding of the psychic background. It frequently happens that the history alone makes it possible for the physician to make a tentative diagnosis of an infectious (chiefly bronchitis) asthma, dust asthma, pollen asthma, or some other type, thus enabling him to decide on tests along certain definite lines

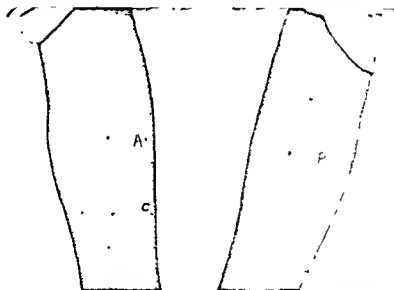


FIG. 295 SKIN TESTS WITH ASPERGILLUS (A) AND PENICILLIUM (P) IN ASTHMA CASE

C = control with normal saline solution. Specificity of test in this case was proved by focal reaction (i.e. attack of asthma)

cause of the asthma, and this involves finding both the exciting and the predisposing factors (see section on etiology). Furthermore, it is essential to determine whether the case is one of allergic or of pathergic origin. In both instances it is of special importance to determine whether the etiologic agents are exogenous or endogenous in character. To achieve these aims, the following approaches are available.

HISTORY

Here, as in all other allergic conditions, the history is of the very greatest importance. The questionnaire to be found in the Appendix gives a detailed outline of the many pertinent questions that apply, the answers to which may yield invaluable hints as to the nature of

SKIN TESTS

As for skin tests, we can be very brief, since the entire subject has been discussed in considerable detail elsewhere (p 157). In a word, it may be said that both positive and negative tests are to be interpreted from a highly critical viewpoint. The writers unconditionally accept as specifically positive only those tests that actually induce an asthmatic attack (FIG. 295). This occurred in only 9 per cent of our material, consisting of 452 cases. Moreover, failure to elicit a cutaneous reaction does not exclude the possibility that the substance tested is indeed the causal agent; a negative test may be due to the fact that not the skin but the bronchial mucosa is the shock organ, or that the protein

used for the skin test, particularly if it is of bacterial origin, may have been chemically altered to such an extent that it is no longer identical with the protein responsible for the asthmatic seizure

A special problem is that of proper evaluation of skin tests in bacterial or infectious asthma. As mentioned on page 437, there are two schools of thought on this question. Some regard a positive, others a negative reaction as specific. The present writers are emphatically of the opinion that the decisive point is the elicitation of a focal reaction in the form of increased bronchial secretion, or even exacerbation or elicitation of asthmatic manifestations. Such responses are usually accompanied by marked local skin reactions, but these are sometimes lacking. This might possibly be explained by the fact that there is a hypersensitiveness to bacterial protein in the former case, while in the latter the hypersensitiveness is in relation to bacterial toxin (as in the Schick or Dick reactions)

BRONCHIAL TESTS

These include inhalation or spray with a specific dust or other substance, and are quite often positive in cases that do not present any reaction to skin tests. For example, we found positive bronchial tests in 8 cases (to flour, house dust, leather dust, straw, ipecac, goose feathers, sesame oil, and acacia flowers). Similar findings have been reported by Stevens.⁷²⁸

The *environmental test* is also to be regarded as a bronchial test. This consists in actual exposure, under ordinary conditions, to the suspected agent. It may be divided into day and night tests. Illustrative instances in which environmental tests were essential in establishing the diagnosis included cases in which attacks were elicited when the patients visited their places of occupation, such as barley warehouses, sesame oil factories, leather goods plants, and fur factories. Furthermore, quite a few reacted only to night tests, chiefly owing to mattresses or pillows on their beds, or fungus growing in the bedding.

NASAL TESTS

These are particularly helpful in cases of asthma due to pollen or flour

ORAL TESTS

In cases of allergic asthma due to ingestants, oral testing is the method of choice. Rackemann⁷²⁹ has pointed out that skin tests fail to elicit reactions in two-thirds of all cases of nutritive asthma.

It may be of interest to note that by means of all the aforementioned tests, we were able to determine the causation in 128 (28.3 per cent) of a series of 452 cases. This was accomplished by intracutaneous tests in 37 cases, by nasal tests in 54, by environmental tests in 29, and by bronchial tests in 8 cases.

17 THERAPY

In practice, one must distinguish between the treatment of an asthmatic attack as a symptom and of the asthmatic condition as a disease, the therapeutic approach to the former will usually be symptomatic while the latter problem will often call for consideration from the etiologic viewpoint.

The treatment of asthma may therefore, be divided as follows: (1) measures to combat the asthmatic attack, (2) prophylactic and curative measures to prevent attacks in the future, and (3) determination and, if possible, elimination of predisposing or contributory causes.

It should be stated, first of all, that just as is done in the case of diabetes, every severe case of asthma should be hospitalized for at least a few days, in order to determine the pathogenesis of the condition. In this way, all the necessary studies—allergy tests, roentgenograms, electrocardiograms, sinus examination, bacteriologic investigation—can be conveniently carried out, moreover, the patient's response to therapy can best be observed under these conditions and the family physician will then be able to handle the case along the lines found most effective by these investigations. Extensive experience has convinced the writers that close cooperation between the allergist and the family doctor often produces satisfactory results even in cases that seem almost hopeless.

a) TREATMENT OF THE ASTHMATIC ATTACK

For purely didactic reasons, the treatment of the acute attack, of status asthmaticus,

and of the chronic stage will be discussed separately, although the use of certain drugs, particularly epinephrine and aminophylline, is of course common to all of them. Nevertheless, certain difficulties peculiar to each of the phases and the means by which they may be overcome, warrant individual discussion of the therapy of each.

As for the treatment of the acute attack and of status asthmaticus, we shall mention only those emergency measures that the physician must employ promptly. Needless to say, when there is any reason to suspect clinically, or on the basis of tests, the presence of hypersensitiveness to some inhalant or ingestant, this substance must be immediately eliminated.

(1) *The Acute Attack*

The first and most important problem is to rid the patient of his severe dyspnea. For this purpose, *epinephrine hydrochloride*, in a 1:1,000 solution, administered subcutaneously, is the sovereign remedy. The dose required for relaxation of the bronchospasm by sympathomimetic stimulation depends on the severity of the attack, on the duration of the disease, and on the patient's previous responses to this drug. Since epinephrine is purchasable in 1 cc. vials, the entire contents of the ampule are usually injected at once, with the result that in very many patients highly unpleasant symptoms are produced, such as severe palpitation, precordial distress, trembling, marked pallor, feeling of weakness, and severe nervousness. As a modification of Hurst and Bray's method, the present writers suggest beginning with 0.2 cc. (3 minims) subcutaneously, leaving the injection needle in the skin, and then administering the same dose at intervals of from three to five minutes until the patient feels very much better. Aside from the fact that this fractional dosage method rarely brings on such strong reactions—if, indeed, any untoward effects—a total dose of about 0.6 cc. very frequently suffices to free the patient of his symptoms. Moreover, this cautious approach is absolutely essential in dealing with children.

Since the attacks so commonly make their appearance suddenly, and especially at night, it is well to teach the patient or someone in his

environment the technic of giving injections. However, he should be instructed not to use it unnecessarily. Although epinephrine is not habit-forming, patients not uncommonly give themselves injections more frequently than is perhaps necessary, they do this because they are afraid the injection may not work as promptly and effectively later, at the height of the attack. One occasionally observes severe local skin damage attributable to the drug's ischemic effect on the local blood vessels, when it is injected too superficially (Fig. 296).

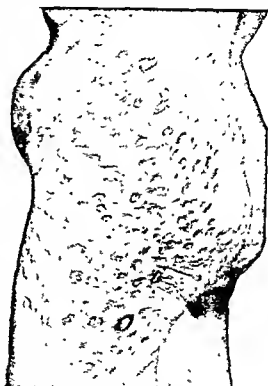


FIG. 296 NECROSIS AND SCARRING IN ASTHMATIC CASE DUE TO EPINEPHRINE (ADRENALIN)

Otherwise, however, it is surprising to note what quantities of adrenalin people can take over long periods of time without suffering any damage to the heart or vascular system. Thus, Rackemann and Theiler²²⁹ observed a patient who consumed 280 bottles of 30 cc. each in the course of three years, and Waldbott²³⁰ mentions 2 patients who gave themselves a daily total of 30 cc. and 37.5 cc., respectively, for many weeks.

²²⁹ * Idem, and THEILER, H. *ibid.* 7: 323, 1936.

²³⁰ WALDBOTT, G. L. *J. A. M. A.* 110: 1423, 1938.

In patients with hypertension it is advisable to make sure that this treatment does not unduly elevate the blood pressure. Some rare cases have been observed (Keeney,²⁸) in which an injection brought on a violent splitting headache followed by unconsciousness. These manifestations are probably due to cerebral angiospasm or vascular hemorrhage resulting from the sudden hypertension. It is generally assumed that this followed the accidental entrance of epinephrine into a small vessel. However subcutaneous injections can also bring on manifestations of the greatest severity particularly acute angina pectoris and even death. The minimal lethal dose by the subcutaneous route seems to be approximately 10 mg. Gormsen^{29,30} recently reviewed 29 cases of fatal epinephrine reactions. In a case described by him the patient accidentally gave himself an injection of 1 cc. of a 1:100 instead of a 1:1000 epinephrine solution.

The unpleasant after effects not to mention the serious sequelae can be avoided by inhaling instead of injecting the adrenalin. Ever since Graeser and Rowe³¹ introduced the 1:100 epinephrine solution it has been found that in the majority of cases inhalation gives results similar to those achieved by injection—provided a suitable nebulizer is employed (that is an all glass or all plastic apparatus that vaporizes the solution completely without forming any droplets) and provided it is used before the attacks are too far advanced. Furthermore the convenience of this method permitting the patient to get adequate relief wherever he may be and the psychologic factor inherent in the fact that he has at his command a method upon which he can rely are additional advantages that can not be overlooked. However at the height of an asthmatic attack it may be necessary to administer a small dose of epinephrine hypodermically followed by inhalation if the beneficial effect of the injection seems to be wearing off.

It is essential that the physician give the patient precise instructions as to how the apparatus is to be used. The mouthpiece is

inserted into the mouth just past the teeth but *the lips must remain open*. Then the patient must be taught to squeeze the bulb of the atomizer at the moment of a deep inspiration so as to bring the drug into direct contact with the bronchial mucosa. This procedure should be repeated once or twice but no more than necessary to obtain relief.

Moderate dryness and irritation of the throat are quite commonly noted. This may be avoided or at least considerably lessened by gargling with water or isotonic saline solution immediately after the inhalation or by swallowing a few drams of warm glycerin. Lockey³² incorporates 5 per cent glycerin in the epinephrine solution.

The hand vaporizer has some disadvantages. The squeezing of the bulb and the repeated deep inhalations may be exhausting to a patient who is very ill or dyspneic. Richards and his associates^{33,34} therefore suggested a technic for continuous inhalation consisting of the use of a tank of oxygen with the usual reducing valve to regulate the flow of gas through a glass nebulizer. With this method 1 cc. of solution is vaporized in three to ten minutes and the patient simply breathes quietly during this time. Intermittent epinephrine vaporization combined with helium oxygen inhalation (Wickner³⁵) and continuous nebulization of glycerinated epinephrine solution using a mixture of 10 per cent carbon dioxide for its expectorant effect and 90 per cent oxygen as the gas (Lockey^{36,37}) are said to be particularly efficacious.

The effect of epinephrine which sets in very quickly but soon vanishes can be considerably and advantageously increased by the longer lasting *ephedrine* which by itself is ineffective in severe attacks. Doses ranging from 0.025 to 0.045 Gm. ($\frac{3}{8}$ to $\frac{1}{2}$ grain) of ephedrine sulfate are recommended. If it is desired to postpone the onset of action of the drug so as to prevent asthma spells from awakening the patient during the night one may give enteric coated ephedrine tablets or some ephedrine theophylline compound such as Luasmin. For patients who cannot tolerate ephedrine

²⁸ LOCKEY S. D. *ibid* 14:38, 1943.

²⁹ RICHARDS D. W. JR., BARACH A. L. and CROWELL H. A. *Am J M Sc* 199:22, 1940.

³⁰ WICKNER I. *Ann Allergy* 3:187, 1945.

³¹ LOCKEY S. D. *ibid* 3:362, 1941.

²⁸ KEENEY E. L. *ibid* 112:2131, 1939.

²⁹ GORMSEN H. *Ugeskr f Læger* 101:242, 1939.

³⁰ GRAESER J. B. and ROWE A. H. *J Allergy* 6:415, 1953.

propadrine hydrochloride in the same dosage is a useful substitute (Murphy²²⁸⁵). Other sympathomimetic drugs which have been recently reported to be effective in terminating asthmatic paroxysms include nethamine 0.050 Gm or $\frac{3}{4}$ gr. (Friedman and Cohen²²⁸⁶); nethacatin, a combination of nethamine and acetophenetidine (Craddock²²⁸⁷), nethamine hydrochloride and theophylline isobutanolamine, which can also be given intravenously, intramuscularly, or by rectal suppositories in severe cases (Hansel²²⁸⁸), and by injection, ethylorsuprenen (Tainter et al.²²⁸⁹ Hartman²²⁹⁰), and 1-(3,4-hydroxyphenyl)-2 amino-1-butanol (Suter and Ruddy²²⁹¹), which are said to be as effective as epinephrine.

"During the past few years, a number of authors (Efron,²²⁹² Brown,²²⁹³ Rowe,²²⁹⁴ Kahn,²²⁹⁵ Piness,²²⁹⁶ Rackemann,²²⁹⁷ and Urbach, Loew, and Gottlieb²²⁹⁸) have demonstrated that slow intravenous injection of aminophylline (theophylline ethylenediamine) is a most effective, prompt, reliable, and safe therapeutic procedure for combating asthmatic attacks, even after the patient has become refractory to adrenalin. Moreover, aminophylline seems to restore the body's responsiveness to adrenalin in practically all cases that have become adrenalin-fast (Herrmann and Aynesworth²²⁹⁹). The exact mode of action of this drug is still in controversy. Its beneficial effect is generally attributed to an antispasmodic action—i.e., relaxation of the spastically contracted circular muscles of the bronchi, thereby re-establishing the normal diameter of the lumen and thus permitting free passage of air to and from the lungs. However, on the basis of their observations of its effect on blood pressure fluctuations, Osgood and

Ehret²³⁰⁰ believe that the favorable action of aminophylline is effected by increasing the blood flow through the pulmonary circulation by vasodilatation, and that its bronchodilating effect is of secondary importance. To achieve an immediate effect, 0.24 Gm. ($3\frac{3}{4}$ grains) of aminophylline diluted in 10 cc. of saline, or better of 10 per cent glucose, should be given intravenously. In very severe cases, it may be necessary to give 0.48 Gm. ($7\frac{1}{2}$ grains) dissolved in 20 cc. It is absolutely essential to take as long as five minutes to administer the solution in order to avoid a "speed shock." Care should be taken to prevent extravasation into the perivascular tissues; the injection of novocain is required to control the pain following such an accident. Intramuscular administration of aminophylline is too painful. The untoward effects of the drug include an initial hyperpnea, a feeling of warmth, particularly in the face, a burning sensation in the eyes, a metallic taste, and occasionally nausea and vomiting. Merrill²³⁰¹ has reported dangerous and even fatal reactions to intravenous aminophylline in cases of bronchial asthma, but these appear to be largely confined to those with associated cardiac decompensation, hypertension, or otherwise *in extremis*. Certainly, properly administered, the drug can be, and on innumerable occasions has been given with excellent results and without noteworthy side-effects.

Barach²³⁰² employed rectal instillation of 0.5 Gm. of aminophylline dissolved at the time of administration in 20 cc. of tap water, and given by means of a No. 12 French rubber catheter and a 20 cc. glass or rubber bulb syringe. This technique can be readily taught to the patient or relatives. The relief of asthma is not as rapid as with the intravenous route, but in most instances relaxation of bronchial spasm takes place within ten to thirty minutes. Nausea and vomiting may occur after large doses, but the circulatory side-effects of rapid intravenous injection, such as dizziness and faintness, are rarely encountered and never troublesome. We found this method very valuable and rather effective even when used repeatedly for weeks.

²²⁸⁵ Murphy, J. A. *Pennsylvania M J* 43, 65, 1909.

²²⁸⁶ Craddock, W. H. *J Med (Cincinnati)* 27, 457, 1911.

²²⁸⁷ Tainter, M. L., Calkins, W. M., Weissell, L. J., and Hartman, M. M. *J Pharmacol & Exper Therap* 84: 269, 1914.

²²⁸⁸ Hansel, M. M. *Ann Allergy* 3, 506, 1915.

²²⁸⁹ Suter, C. M., and Ruddy, A. W. *J Am Chem Soc* 66, 741, 1944.

²²⁹⁰ Efron, B. G. discussion to Tuft, L., and Brodsky, M. L. *J Allergy* 7, 249, 1936.

²²⁹¹ Brown, G. T. *J Allergy* 10, 64, 1935.

²²⁹² Rowe, A. H. *J A M A* 111, 1472, 1935.

²²⁹³ Kahn, I. S. *Tr State M J* 11, 224, 1939.

²²⁹⁴ Piness, G., and discussors. *J Allergy* 10, 270, 1939.

²²⁹⁵ Rackemann, F. M. *J A M A* 114, 1958, 1940.

²²⁹⁶ Herrmann, G., and Aynesworth, M. B. *J Lab & Clin Med* 23, 135, 1937.

²²⁹⁷ Osgood, H., and Ehret, F. E. *ibid* 28, 1415, 1941.

²²⁹⁸ Merrill, G. A. *J A M A* 123, 1115, 1941.

²²⁹⁹ Barach, A. L. *J Allergy* 14: 296, 1943.

²³⁰⁰ *Idem*. *J A M A* 128, 339, 1945.

Maisel and Somkin²³⁰⁴ and Melton²³⁰⁵ reported control of severe asthmatic paroxysms by intravenous injection of 0.05 to 0.1 Gm of *nicotinic acid*. Relief is obtained within three to five minutes and seems to coincide with the appearance of a flush. It is presumably due to the marked vasodilating properties of the drug. Oral administration (0.2 Gm) is somewhat less effective.

Maletta²³⁰⁶ found that intramuscular injection of 2 cc doses of a mixture of equal parts of *ether* and peanut oil produced relief in stubborn cases of asthma. Although the injection caused temporary burning pain no induration or abscess resulted. The taste and smell of ether persisted as long as a day. Epinephrine fast patients were noted to respond again. The dose may be repeated in several hours as indicated.

Intravenous administration of *magnesium sulfate* may also control severe seizures. As shown by Haury,²³⁰⁷ this has a bronchodilating effect on the isolated lungs of guinea pigs. Rosello and Pla²³⁰⁸ among others employed it clinically in doses of 10 cc of a 10 per cent solution intravenously. Lumière²³⁰⁹ recommended magnesium hyposulfite in the same dosage.

(2) Status Asthmaticus

The physician called in to treat a patient suffering from status asthmaticus will naturally first try *epinephrine* subcutaneously and aminophylline intravenously. Regrettably however this type of treatment often brings only temporary relief in this severe condition. In order to prolong the effect of the drug Keeney^{8,9} has suggested the use of epinephrine suspended in sterile peanut oil each cubic centimeter containing 2 mg. of the drug. Doses of from 0.5 to 1.5 cc. are injected intramuscularly. While this method has been found very satisfactory for some patients it has elicited in others severe local reactions, some of which were found to be due to sensitization to peanut

oil. Moreover Cohn²³¹⁰ described untoward symptoms resembling shock and accompanied by vomiting and chills. For these reasons many investigators have been trying to find another menstruum such as gelatin and anhydrous wool fat but without any striking results.

For patients with intractable asthma who fail to obtain relief with the usual epinephrine preparations Kenney²³¹¹ recommended intravenous injections of 100 cc of 50 per cent sucrose with 0.5 cc of 1:1000 epinephrine added. Since this concentration of sugar may be irritating to the vein Rackemann²³⁰⁸ prefers intravenous infusion of a liter of 5 per cent solution of dextrose or of a physiologic solution of sodium chloride to which 1 to 2 cc of 1:1000 epinephrine is added and thoroughly mixed. The venoclysis should be given slowly so that it takes at least one hour. If no benefit ensues from 1 to 2.5 cc of 1:1000 epinephrine (a 1:1000 solution diluted ten times) may be injected intravenously. This should be stopped immediately if the first signs of adrenergic symptoms are noticed (pallor, tremor, perspiration, headache, cardiac oppression). Kahn²³² has made the interesting observation that after such a reaction subcutaneously administered doses of epinephrine regain their lost effectiveness.

Demerol (isonipecaine) in doses of 25 to 100 mg subcutaneously or intramuscularly or 100 mg by mouth has been shown to be quite effective in status asthmaticus (Batterman and Himmelstach^{8,6}; Noth, Hecht and Yonkman^{8,5}; Douthwaite²³¹³; Barach²³¹⁴; and Hepburn²³¹⁵). Good results have also been obtained when it is administered in a mixture with half the usual amount of epinephrine. The usual side effects are dizziness, nausea, euphoria, headache, and dryness of the mouth. However severe systemic reactions have been observed by Noth et al.^{8,5} Hobbs²³¹⁶ and Forman²³¹⁷. Contrary to most investigators

²³⁰⁴ MAISEL F. E. and SOMKIN E. J. *Allergy* 13: 397, 1942.

²³⁰⁵ MELTON G. B. *J. M. J.* 1: 600, 1943.

²³⁰⁶ MAIETTA A. L. *New England J. Med.* 227: 985, 1942.

²³⁰⁷ HAURY V. G. *J. Pharmacol. & Exper. Ther.* 64: 58, 1938.

²³⁰⁸ ROSELLO H. J. and PLA J. C. *Prensa méd. argent.* 23: 1677, 1936.

²³⁰⁹ LUMIÈRE A. and MALESPIÈRE. *Compt. rend. Soc. de biol.* 100: 351, 1929.

⁸ COHN J. J. *Allergy* 10: 49, 1939.

⁹ KEENEY E. L. *Bull. Johns Hopkins Hosp.* 66: 34, 1940.

²³¹⁰ KAHN I. S. *Ann. Int. Med.* 3: 1140, 1930.

²³¹¹ DOUTHWAITE A. H. *B. M. J.* 2: 200, 1944.

²³¹² BARACH A. L. *Bull. New York Acad. Med.* 20: 545, 1944.

²³¹³ HEPBURN J. B. *J. M. J.* 1: 174, 1945.

²³¹⁴ HOBBS F. B. *ibid.* 2: 328, 1944.

²³¹⁵ FORMAN J. *Letters Internat. Corr. Club of Allergy Ser.* 8: 83, 1945.

Forman feels that it is effective in milder cases but not in the severe type.

If the various forms of epinephrine therapy and aminophylline injections fail to bring relief, the situation must be regarded as dangerous. In such cases, oxygen is sometimes helpful, administered either in an oxygen tent or preferably by means of the BLB mask, or the Barach-Eckmann injector meter mask. Standards for the effective administration of inhalation therapy have been laid down by the New York Academy of Medicine.²³¹⁸ However, Comroe et al.²³¹⁹ showed that while 100 per cent oxygen may be safely given for short periods, its use in excess of twelve hours very frequently causes untoward effects. Moreover, as Barach²³²⁰ has shown, a mixture of 80 per cent helium and 20 per cent oxygen, inhaled through a specially designed apparatus, is much more effective. All leaks in the mask must be carefully and completely closed, because of the tendency of the gas to escape through the most minute openings. Inhalation of the oxygen-helium mixture serves, above all, to combat the anoxemia, exhaustion, and apprehension. When the terminal bronchioles are nearly closed by edema or spasm, the smaller, rapidly moving helium molecules can more readily diffuse in and out of the alveoli. By substituting helium for nitrogen in the air, the motility of the mixture is increased almost three times, since the specific gravity of helium is one-seventh that of nitrogen. Cyanosis is lessened, and breathing is accomplished with much less effort, allowing relaxation and rest for the patient. In severe stages, the patient should be given 6 liters of the mixture per minute. After a while the proportion of helium to oxygen may be changed toward an increase in the latter, until finally oxygen alone is used during the recovery phase. While the cyanosis and respiratory difficulty are usually eliminated in a relatively short time, it takes from twenty-four to forty-eight hours to control the bronchial spasm in extreme cases (Maytym²³²¹). It is important to note that adrenalin-fast patients often be-

come responsive to epinephrine after prolonged helium-oxygen inhalations. The disadvantage inherent in this treatment is that, even in times of peace, the price of helium has always been prohibitive for extensive use. Segal²³²² has shown that positive pressure oxygen-helium therapy can be effectively combined with continuous vaporization spray of neosynephrin, vaponephrin, aminophylline, or micro-crystalline sulfathiazole in indicated cases.

Barach²³²⁰ ²³¹⁴ has advocated a combined therapy intended to produce repeated bronchial relaxation in intractable asthma in the belief that if a vicious cycle of persisting spasm of the circular bronchial musculature can be overcome for a five to ten day period, prolonged freedom from severe asthma should result. Appropriate drug and inhalational therapy promoting relaxation of the constricted bronchial musculature is employed in order to reduce the undesirable increase in the negativity of the intrapulmonary pressure during the inspiratory cycle which is present in obstructive dyspnea and which exercises a harmful influence on respiratory function. A summation effect is achieved by employing the following procedures on hospitalized patients: rectal administration of 0.5 Gm. of aminophylline once or twice daily for a period of one to three weeks, inhalation of helium-oxygen mixtures for one to six hours daily for five days, dilaudid in some cases, given in the rectal aminophylline solution, continuous ingestion of potassium iodide in doses of 1 to 3 cc. daily, inhalation of a nebulized spray of 1:100 epinephrine (or 1 per cent neosynephrin) one to five times daily, and sedation, preferably with sodium phenobarbital (0.1 to 0.2 Gm. by injection once or twice daily). Hypodermic injections of epinephrine are used only if the inhalation method fails. Prolonged rectal aminophylline instillation is indicated in those patients with intractable asthma who also have marked functional pulmonary emphysema.

Since the accumulation of very viscid secretions in the lumen of the large as well as the small bronchi is not uncommonly the cause of intractable asthma, bronchoscopic therapy may

²³¹⁸ Committee on Public Health Relations, New York Academy of Med. J. A. M. A. 121: 755, 1943

²³¹⁹ COMROE, J. H., DRIPPS, R. D., DICKER, P. R., and DERING, M. *ibid.* 128: 710, 1943

²³²⁰ BARACH, A. L. *Ann. Int. Med.* 9: 739, 1935

²³²¹ MAYTUM, C. K. *J. Allergy* 10: 264, 1939

²³²² SEGAL, M. S. *New England J. Med.* 231: 533, 1944

be a life saving measure (Lukens²³⁵ Clerf²³⁴ Andrews²³⁶ Bases and Kurtin²¹ Hilding¹⁶⁸). The trachea and bronchi down to the fourth and fifth order can be cleared of secretions under direct vision by suction through the bronchoscope. Because of the tenacious character of the mucus plugs obstructing the lumens of the smaller bronchi may also be removed in this manner. This treatment should be followed by intravenous injection of sodium iodide (1 Gm in 10 cc of distilled water) once or twice daily over a period of several days in order to liquefy the secretions and thus facilitate expectoration. In dehydrated patients intravenous administration of 1 000 cc of 10 per cent glucose in saline may further decrease the viscosity of the bronchial secretions.

The writers found *enesection* (400 to 500 cc) to be helpful possibly because it diminishes the congestion of the lungs as well as because of its beneficial effect on the circulation. The pulmonary congestion can also be combated by intravenous injections of 50 cc of a 25 or 50 per cent dextrose or sucrose solution.

In cases of status asthmaticus resulting from respiratory infection specific chemotherapy in the form of *sulfonamides* offers possibility of relief according to Weil and Climo²³⁵ Oatway²³⁷ and Bell²³⁸. Nebulized solutions of sulfonamides for inhalation have also been successfully used in such cases to attain a maximum concentration of the drugs where their greatest action is desired—at the bronchial mucous membrane. Stacey²³⁹ and Applebaum²⁴⁰ employed a 5 per cent sodium sulfathiazole solution in a nebulizer through which oxygen was permitted to flow at the rate of 4 liters per minute. The patient held the nozzle of the nebulizer between his teeth and breathed through the open mouth for twenty minutes. Treatments were given three times a day for an average of ten consecutive days using about 2 cc of solution

each time. Applebaum reported that 8 of 12 cases with infectious asthma showed moderate or marked improvement. Bronchitis and bronchiectasis also responded to this therapy. Mutch²⁴¹ similarly employed a 50 per cent solution of sulfonamide E O S and Segal²⁴² microcrystalline sulfathiazole nebulized by means of oxygen. Other gas mixtures such as carbon dioxide oxygen for its expectorant effect or helium oxygen may be substituted or vasoconstrictor drugs added to the solution.

Intramuscular injection of *penicillin* has been used in the treatment of asthma due to primary bronchial infection (bacterial allergy). Schonwald and Deppe²⁴³ reported marked improvement in 69 cases of asthma. Leopold and Cooke²⁴⁴ complete remission of symptoms in 2 patients with intractable continuous asthma and Derbes and Wilson²⁴⁵ considerable benefit in 2 cases. On the other hand careful evaluation of the results in 9 cases led Hampton and his colleagues²⁴⁶ to the conclusion that while slight clinical improvement occurred in some of their cases penicillin is of little or no value in the treatment of intrinsic asthma. We have also failed to note definite benefit from injections of penicillin in asthma.

Inhalation of penicillin aerosol has been employed with favorable results by Barach²⁴⁷ Hagens²⁴⁸ and their colleagues Vermilye²⁴⁹ and ourselves. Solutions of sodium penicillin containing from 8 000 to 100 000 units per cc are nebulized in a fine mist (particles smaller than 1 micron) and inhaled several times a day. The drug can be demonstrated in the blood and a considerable portion recovered from the urine.

TECHNIC OF INHALATION OF PENICILLIN AEROSOL. From 0.5 to 1.0 cc of a solution containing 20 000 to 50 000 units of penicillin sodium is placed in a properly constructed nebulizer* the end of which is held with a

²³⁵ LUKENS R M. *Laryngoscope* 35: 22, 1925.

²³⁴ CLERF L H. *Ann Int Med* 9: 1050, 1936.

²³⁶ ANDREWS A H. *Jr* 1: 505, *M J* 3: 2, 1938.

²³⁵ WEIL C K and CLIMO H J. *J N A Alabama* 9: 30, 1940.

²³⁷ OATWAY W H. *Jr* *A Cons Med* 1: 194, 1941.

²³⁸ BELL W W. *Canad M A J* 52: 504, 1945.

²³⁹ STACEY J W. *D S Chest* 9: 302, 1943.

²⁴⁰ APPLEBAUM I L. *Id* 10: 415, 1944.

²⁴¹ MUTCH N. *Lancet* 2: 775, 1944.

²⁴² SCHONWALD P and DEPPE E F. *Northwest Med* 44: 10, 1944.

²⁴³ LEOPOLD S S and COOKE R A. *Am J M S* 209: 84, 1944.

²⁴⁴ DERBES A J and WILSON J L. *Ann All* 33: 204, 1945.

²⁴⁵ HAMPTON S F, WINE M B, ALLEN W, THOMPSON C S and STARR M P. *J A M A* 127: 1108, 1945.

²⁴⁶ BARACH A L, SLEERSTEIN F H, OPPENHEIMER E T, H YER T and SORACE M. *Ann Int Med* 22: 485, 1944.

²⁴⁷ HAGENS E W, KARP M and FARMER C J. *J Clin Otolaryng* 4: 319, 1945.

²⁴⁸ VERMILYIE H N. *J A M A* 129: 250, 1945.

*Vaponeph in or DeVilbiss No. 40.

the partly opened mouth and which is operated by compressed oxygen at a rate of 5 to 8 liters per minute (FIG. 296A). A glass or metal Y tube is inserted in the line between the oxygen tank and the nebulizer, the open end being closed by the patient or nurse only during inspiration, forcing the oxygen stream through the nebulizer. During expiration the oxygen is diverted into the atmosphere, thereby conserving penicillin. The patient is instructed to breathe deeply and to hold his breath each time as long as possible in order to favor the maximum deposition of the fog droplets in the bronchioles. (However, some authorities feel that ordinary respiration is preferable to prevent absorption of the drug from the expanded alveolar surface.) The cycle is repeated until the total amount of the drug is nebulized. Treatments are given every three or four hours during the day for several days,



FIG. 296A. PENICILLIN AERO-OL INHALATOR

Same apparatus may also be used with epinephrine and other drugs effective by inhalation.

(Courtesy, Ohio Chemical Co.)

or less often in milder cases. The technic is readily learned by patients, even young children, and treatments may be administered at home, employing a portable apparatus. For the treatment of infants, the nebulized spray may be directed through a positive-pressure face mask.

Of 8 patients treated by Barach,²²⁶ all showed improvement but recurrence took place in 4 within one month after treatment. Vermilye²²⁷ feels that this treatment should be given before a severe intractable stage is reached and advises a prolonged course. He advocates this therapy in the following conditions, among others: persistent bacterial infections of the upper respiratory tract which develop into

bacterial allergies in the constitutionally non-allergic patient, upper respiratory bacterial infections which develop into bacterial allergies in individuals who have an allergic type of constitution in combination with other extrinsic allergies, such as sinobronchitis, dermatitis, asthma, and migraine; and chronic upper respiratory infections with acute fatigue persisting for years in allergic and nonallergic subjects. Untoward effects are usually insignificant, and may consist of soreness under the sternum, coughing, mild urticaria, or sore throat. However, Vermilye noted that if aerosol penicillin is given simultaneously or within a few hours of a pollen or vaccine injection, severe reactions may develop, characterized by acute abdominal pain, restlessness, urticaria, and angioneurotic edema. Hampton and his co-workers²²⁸ felt that intratracheal penicillin was of little value, but they did not employ an aerosol. The junior author can confirm the lack of efficacy of unnebulized intratracheal penicillin.

It should be clearly understood, however, that while the inhalation of penicillin aerosol is very valuable in combating any existing chronic or acute infection with staphylococcus or streptococcus, this antibiotic is only bacteriostatic and not bactericidal. In other words, if a chronic bronchial infection is the basis of the infectious bronchitis asthma, this condition will recur to some extent a few weeks after penicillin therapy is stopped. On the other hand, we found penicillin of great help in those cases of asthma which were superimposed on acute bronchial or sinus infection.

Prolonged administration of oral penicillin for the prevention of recurrences of bacterial asthma and asthmatic bronchitis has been suggested, and employed successfully in 1 case (Gyorgy et al.²²⁹), but requires further trial.

When all other measures prove unavailing, *anesthesia* may be tried as a last resort. Rectal ether is the least dangerous. By means of an egg beater, 2 ounces of surgical ether and 4 ounces of olive oil are whipped for from one to two minutes until a clear, golden-brown liquid is produced. (Only olive oil is to be

²²⁶ GABRY, P., EVANS, K. W., ROSE, E. K., PERLINGHERO, J. G., and ELIAS, W. F. *Pennsylvania M J* 49: 409, 1946.

used, cottonseed oil and peanut oil must be avoided because of the danger of encountering a pre existing hypersensitiveness to them) The liquid is then introduced slowly (taking about twenty minutes) into the rectum through a tube children should be given one half or less of this dose depending on the body weight According to Kahn,²³⁰ small doses are ineffective, since a relatively deep narcosis must be reached Excitement and vomiting are rarely seen during the anesthesia However, bronchial relaxation does not always follow, but one half to one hour later epinephrine is usually again found to be effective Fuchs²³¹ and Thomas²³² often found rectal administration of avertin (tribromethanol in amylene hydrate), in doses of 60 to 90 mg per kilogram of body weight, to be particularly effective Intravenous injections of nuke thamide (coramine) will usually counteract the effects of avertin and bring the patient out of anesthesia An antispasmodic effect can also be obtained with cyclopropane anesthesia (Meyer and Schotz²³³ Sweatman²³⁴) A similar result may be achieved by chloral hydrate (0.65 to 2.0 Gm, or 10 to 30 grains preferably the smaller dose repeated every six hours) or paraldehyde (4 to 8 cc, or 1 to 2 drams) The soporific effect comes on almost immediately, and within five or six minutes the patient will suddenly relax Care should be exercised however with respect to the depressant action of the latter drug on the central nervous system Hartman²³⁵ advocates intramuscular injection of 30 to 80 mg of papaverine hydrochloride Although this drug is derived from the same plant as is opium it does not have the latter's depressant effect on respiration, but exerts a markedly relaxing influence on the smooth muscles

Another way to induce relaxation was first suggested by Wassermann²³⁶ Proceeding on the assumption that paroxysmal dyspnea is frequently brought on by a reflex mechanism, he recommends unilateral pressure on the carotid, thereby producing vagal stimulation

TECHNIC With the patient lying supine his chin slightly elevated the position of the carotid is determined then placing the hand flat under the patient's neck in order to give firm support one presses the thumb of the same hand against the right carotid The duration and the intensity of the pressure depend on the response actually produced usually requiring from three to eight seconds It is recognized by the appearance of bradycardia When pressure is successful the attack ceases most abruptly and the cyanosis and swelling of the face also disappear The overdistended thorax literally collapses in a series of jerky exhalations

Needless to say the duration of the symptom free period is limited (from a half hour to a few days), nor can relief be obtained in this manner in every case Many patients report that the carotid pressure method is very painful and it is also not without danger

It is interesting to note that for intractable cases Thewlis²³⁷ recommends the use of *alcohol* in its full physiologic action a tablespoonful of whisky or brandy is given every half hour for several doses, and then every two or three hours Piness²³⁷ recommends administration of large doses of *caffeine* in epinephrine resistant cases 2 to 4 grains every two to four hours, by mouth or intramuscularly Strong black coffee may also be given Caffeine should not be given in the evening, however, since it will keep the patient awake

Rackemann²³⁸ has pointed out that the *shock like state* sometimes occurring in severe asthma (or from too much epinephrine) should be treated in the same manner as shock in general Large amounts of plasma glucose, or saline should be given immediately Morphine is contra indicated unless the shock is worse than the asthma and epinephrine may do more harm than good In the so called "counter shock" stage when the asthma is again severe and the patient exhausted and depleted, fluids epinephrine, aminophylline, and oxygen are again indicated

Morphine should be employed only with the greatest possible restraint It depresses respiration, abolishes the cough reflex (a very necessary and protective function), thereby permitting the accumulation of bronchial secretions, it also exerts a definite even though slight, bronchospastic influence (Vaughan and

²³⁰ KAHN I S J Allergy 10 262 1939

²³¹ FUCHS A M ibid 8 340 1937

²³² THOMAS J W Ohio State M J 36 372 1940

²³³ MEYER N E and SCHOTZ S J Allergy 10 236 1939

²³⁴ SWEATMAN C A J South Carolina M A 37 291 1941

²³⁵ HARTMAN M N J Allergy 10 279 1939

²³⁶ WASSERMANN S Klin Wchnschr 9 1121 1930

²³⁷ THEWLIS M W The Care of the Aged St Louis Mosby 1941

²³⁸ RACKEMANN F M M Clin North America 28 1082 1944

Graham²⁵⁴⁹). Piness²⁵⁷ reported 15, Balyeat²⁵⁵⁰ 5, and Unger²¹⁷⁵ 2 cases of death in status asthmaticus following morphine injections. The senior writer saw in consultation a patient who after a morphine injection slept eighteen hours so profoundly that he suffered injury to the nerves of both the right lower and upper extremities, owing to the pressure resulting from an unnatural position. Waldbott²⁵⁵¹ recommends pantopon (0.02 Gm, or $\frac{1}{2}$ grain), in the event that a sedative is imperatively indicated, while Cooke²⁵⁵¹ condones the use of codeine or pantopon in appropriate dosage in children. On the other hand, many experienced authorities strictly forbid the use of any opiate in status asthmaticus, a position to which the present writer emphatically adheres. Demerol in small doses (25 mg. three times a day after meals) has an effective sedative effect without the respiratory depression characteristic of morphine.

Lastly, mention must here be made of the significance of the *psychic factor*. The patient must have complete rest, and visitors should be kept from his room. Furthermore, encouraging words from the physician as regards the condition, and attempts at straightening out unpleasant financial or domestic affairs, are of the utmost importance. Patients with status asthmaticus should unquestionably be hospitalized.

b) PROPHYLAXIS

(1) *Avoidance or Removal of the Specific Cause*

This approach would, of course, constitute the ideal treatment. When a definite substance or substances are discovered or merely seriously suspected of being the causative allergens, the patient must be informed as to just how he can avoid contact with them. This problem of avoiding exposure is, naturally, one that varies from case to case, since it depends on the nature of the allergen and on the patient's living conditions. Although such avoidance is not always an easy matter, it is usually feasible when an exogenous agent is involved. Difficulties are pre-

sented by such a case as that of a farmer, for example, who is hypersensitive to animals that are indispensable to rural economy. It is easier to eliminate exposure to such animal products as hides or the horsehair, down, or feathers in pillows and mattresses. The physician must insist, however, that these substances be removed not only from the patient's bed, but also from the other beds that may be in the same room, and sometimes even from the house, when the hypersensitivity is of high degree. However, it is now possible to cover pillows and mattresses with airtight, impervious materials fastened with zippers (p. 199).

When the hypersensitivity is in relation to some food, its elimination from the patient's diet is not likely to create any hardship, moreover, skeptophylactic treatment, or administration of appropriate propeptans, is also useful in such cases (p. 213).

With the exception of aspirin, drugs with relative infrequency act as the causal agents; when they do, they can usually be replaced by some substitute.

Greater difficulties are encountered when the excitant is associated with the patient's home or occupational environment. When the causal agent is found to be house dust, the procedures discussed on page 200 should be carried out, furthermore, hyposensitization with autogenous house dust should be tried. If molds are found to be the noxious agent, the house should be thoroughly heated through and the moisture eliminated by means of a compressor or some similar method. An effective means of destroying molds is the installation of sterilamps, manufactured by the Westinghouse Electric Company, or the use of Rentschler lamps, as demonstrated by Cadrecha Alvarez²⁵⁵². In addition, the patient should be given a course of injections of mold extracts. If the allergen is somehow connected with the occupational environment (workshop, mill, farm), every attempt must be made to eliminate the excitant by installing ventilation or, preferably, suitable exhausts. It may sometimes be necessary, in the case of persons engaged in certain trades or professions (millers, bakers, furriers, farmers, labo-

²⁵⁴⁹ VAUGHAN, W. T., and GRAHAM, W. R. J. A. M. A. 119: 556, 1942.

²⁵⁵⁰ BALYEAT, R. M. New Orleans M. & S. J. 91, 556, 1939.

²⁵⁵¹ COOKE, R. A. New York State J. Med. 43: 1125, 1943.

²⁵⁵² CADRECHA ALVAREZ, J. Rev. méd. cubana 53: 745, 1942.

ratory workers) for the patient to wear a special mask (Figs 297-298) while at work—or the one devised by Fraenkel²⁵³. It is advisable to have the patient's home or place of work inspected by some competent person e.g., someone trained in industrial medicine or a specially instructed social worker.

If environmental control is of no avail the patient may be obliged as a last resort to change his home, choose another kind of work, or sometimes even move to a different locality.

If circumstances should make it impossible for the patient to change his residence the problem is narrowed down to preparing some

ing of the air by means of water (Leopold and Leopold²⁵⁴) cotton cloth (Cohen²⁵⁵) cellulose (Peshkun²⁵⁶ Rappaport et al²⁵⁷) or fibre glass filters has been suggested by a number of authors. Gay²⁵⁸ and Vaughan²⁵⁹ recommended the use of an air conditioning unit. Crip and Green²⁶⁰ introduced an electrostatic cleaner. The Precipitron (Westinghouse) operating on the last named principle and soon to be made available employed in conjunction with air conditioning is probably the most efficient available combination for home use.

When choosing an occupation the asthmatic individual should avoid any pursuit involving



FIG 297



FIG 298

RESPIRATORS FOR PROTECTION OF ASTHMATICS AGAINST OCCUPATIONAL DUST, ACID VAPORS, AND SIMILAR EXPOSURES

allergen free place for the patient in an otherwise unfavorable environment. The bedroom is of course the most suitable place to be so treated, since the patient normally spends more time there than anywhere else in his home, and since this will at least assure him undisturbed sleep. It also generally serves to lessen the severity of the symptoms that he may suffer in the daytime when he goes about his business. As van Leeuwen⁷²⁸ first pointed out, systematic air purification as obtained by means of a specially constructed allergen free chamber can be most helpful. However, since the cost of installing such an allergen free chamber is prohibitive, the clean

physical or chemical irritation of the mucosa of the respiratory tract, or exposure to hairs, feathers, dyestuffs—in short to substances known to produce asthma in him. Gray and Albert²⁶⁰ hold that allergic patients and those with pre-asthmatic symptoms such as nasal congestion, sneezing, rhinorrhea, cough, or dyspnea, should be excluded from occupations dealing with feathers, furs, or fur dyes, flour, cadmium fumes (electroplating), and

²⁵⁴ LEOPOLD C S and LEOPOLD S S. *J A M A* 84: 731, 1925.

²⁵⁵ COHEN M B. *J Lab & Clin Med* 13: 963, 1928.

²⁵⁶ PESHKUN M M and BECK I. *ibid* 15: 643, 1930.

²⁵⁷ RAPPAPORT B Z, NELSON T and WELKER W H. *J A M A* 98: 1861, 1932.

²⁵⁸ GAY L N. *ibid* 100: 1382, 1933.

²⁵⁹ VAUGHAN W T and COOKEY L E. *J Allergy* 5: 37, 1933.

²⁶⁰ GRAY I and ALBERT M M. *Indust Med* 12: 801, 1943.

insecticides, while Derbes and Winsor²⁰⁹ add that they should not be laboratory workers, food handlers, beauticians, pharmacists, or chemists.

As a matter of principle, the asthmatic individual should sleep alone in a well-aired room. Lack of sufficient relative humidity in overheated homes and other indoor places during the colder months is an important factor in asthma. Before retiring, the patient should, therefore, hang up damp linen cloths in his room, or the air should be kept sufficiently moist by means of a steam vaporizer or electric humidifier. The asthmatic should remove from his bedroom all upholstered furniture, rugs, and other "dust catchers"; the walls should be painted rather than papered. The room must be cleaned only with an electric vacuum cleaner and, if possible, while the patient is out of the house, for the vacuum cleaner bag is often not entirely dust-tight, and it is precisely the finest and lightest particles that are most likely to get out through the fabric. To overcome this difficulty a cleaner (the Rexair) has been devised that removes the dust under water. No animals are to be permitted in the house. The patient and the people living with him are to be warned against bringing street dust into the house with them. It is advisable for very dust-sensitive patients to remove their shoes before entering.

The diet should be selected with a view to the possibility of gastric acidity, which is very common among asthmatic individuals. The acidity is often responsible for flatulence and constipation, which tend to produce attacks by reason of the elevation of the diaphragm. In cases of this sort, thorough examination of the gastro-intestinal tract should be carried out. The patient's food should be readily digestible, and not gas-producing, and he is instructed not to eat too generously, and to masticate thoroughly. Liquids are to be taken only in moderation. Furthermore, the patient should eat very little, if anything, at night, since a full stomach pressing against the diaphragm tends to elicit an attack. Excessive indulgence in alcohol may bring on attacks.

Damp localities—e.g., near lakes, moors, river lowlands, and canals—are generally

unfavorable for asthmatic individuals. Lastly, patients with nonspecific (pathergic) asthma should avoid any irritation of the bronchial mucosa—e.g., sudden changes in temperature, cold winds, dust, tobacco smoke, fumes, noxious gases, insect powders, and strong odors.

(2) *Management of Predisposing and Contributory Factors*

In the section on predisposing and contributory factors in allergy, the significance of these ancillary influences was discussed in some detail. Only a few additional remarks need be made here.

Functional disturbances of the endocrine glands, particularly of the ovaries and of the thyroid, can exert a harmful effect, either through hypo- or hyper-function. Asthmatic attacks are often particularly severe during the menstrual period. The problem of whether this exacerbation is due to the nonspecific effect of nervous tension, which is frequently very marked at this time, or to a specific hypersensitiveness to a hormonal substance, must be studied by appropriate investigation in each case. Two methods are available for this purpose. When the menstrual cycle and flow are in themselves normal, blood should be taken from the patient a few days before the beginning of the period, just at the time when the attacks start or show signs of exacerbation, the serum is then injected intracutaneously every other day during the intermenstruum (for details of technic, see p. 856). If, as a result of these injections, the attacks (as well as the premenstrual tension) fail to occur at the time of subsequent menstruation, the case may be regarded as one of specific endogenous allergic asthma. If, on the other hand, menstrual disturbances can be demonstrated, the physician should institute appropriate hormonal therapy.

Female patients not very uncommonly present hypothyroidism; treatment of this condition with thyroid substances frequently causes a considerable improvement of the asthma condition (Bray¹⁹). A similar statement may be made with respect to hyperthyroidism and its appropriate treatment (Epstein,²²³ Waldbott²²³).

When *gastro-intestinal disturbances* are pres-

ent in a patient with asthma, every attempt must be made to eliminate them. It is especially important to manage constipation, which is very commonly present, preferably by an appropriate diet high in roughage, and "constitutional" walks or massage, rather than laxatives. In cases of an acidity, adequate doses of hydrochloric acid and pepsin are necessary. In the event of an indicanuria, thorough evacuation of the gastro intestinal tract by means of calomel or rhubarb is indicated, at the same time, animal proteins (milk, meat, eggs) and vegetable proteins (green peas, beans) should be excluded from the diet. In cases in which there was a demonstrable connection between asthma and some intestinal condition, Danysz,²³⁶¹ Gottlieb,²³⁶² Hajós,²³⁶³ and Benson²³⁶⁴ prepared stool vaccines and claimed good results with this therapy. It is important to note that only small quantities—e.g., 1,000 organisms—may be injected at the start, to prevent the appearance of severe local, focal, or even general reactions, which the present writers have occasionally seen after larger doses. Danysz also administered orally 50 to 500 mg of bacterial substance dried at a temperature of 60 C., and most enthusiastically praises the results achieved. To what extent these therapeutic results are due to nonspecific protein therapy, or to an antibacterial or antitoxic effect, cannot as yet be determined with any degree of assurance.

Asthmatic attacks can also be produced by *reflex irritation*. While reflexogenic zones are to be found in different parts of the body—e.g., the sexual organs, or the rectum—the ethmoid region is the most important one from this viewpoint, as shown in the section on pathogenesis (p. 584). This reflex irritation seems to be only rarely due to focal infection, and much more commonly to some not very clearly understood form of local nervous irritation, as demonstrated by the fact that cocaineization of this area may abolish the asthmatic attack. Nasal operations are, on the other hand, generally without value.

Cauterization of the nasal mucosa has been recommended time and time again during the past forty years, this procedure is supposed to dull the so called asthmogenic zone in the nose, from which the stimuli go out to the nasopulmonary reflex arc. Many authors cauterize with trichloroacetic acid, others with surgical diathermy or zinc iontophoresis. There can be no doubt that in many cases, and especially in those in which there is a strikingly high degree of irritability of the nasal mucosa, interruption of the reflex arc results in a symptom free period of varying duration, on the other hand, this method is very painful, and its beneficial effects are as a rule ephemeral.

Lastly, one cannot overemphasize the importance of eliminating the *psychic and emotional factors*, such as nervous tension, apprehension, fear, panic, fatigue, emotional upset, mental conflict, and sexual difficulties, in the management of asthmatics. It is, therefore, essential that the physician tactfully ascertain whether the patient as a personality has been affected by some past experience or by some present situation or by anxiety for the future. The psychotherapeutic approach must be adapted to the peculiarities of each patient. The physician can often achieve excellent results by having a man to man talk with the patient or a frank discussion of the problem with someone in the patient's environment. In other cases, distraction through work, charitable activities, sports and similar attempts at sublimation may be very beneficial. Some patients live in fear of an asthmatic attack, especially in the evening, and the resultant anxiety may attain such a degree that it, in turn, is sufficient to evoke paroxysms, it is advisable to give these patients anti asthmatic drugs some hours before the attack is expected. Furthermore, it must be borne in mind that in some instances the asthmatic response represents an 'escape' into sickness, or a means to an end (e.g., dominating the family or, in the case of a child, being sick on particularly difficult days at school). In such cases, psychotherapy, chiefly in the form of persuasion and suggestion, may be helpful—not in the sense that it removes the cause, but rather as part of a re educational program (Ejermann²³⁶⁵).

²³⁶¹ DANYSZ J. *Maladies chroniques non contagieuses*. Paris: Baillière 1920.

²³⁶² GOTTLIEB M. J. *Laryngoscope* 34: 363 1924.

²³⁶³ HAJÓS K. *Klin. Wchnschr.* 10: 1860 1931.

²³⁶⁴ BENSON R. L. J. *Allergy* 2: 152 1934.

²³⁶⁵ EJERMANN C. H. *ibid.* 9: 565 1938.

It is occasionally found necessary to modify the patient's environment, particularly in the case of children of asthmatic parents, for under these circumstances one often observes what is known as "pseudoheredity," that is to say, the child's symptoms are really an imitation of the adult's actual disease. In severe cases of this kind, it may be necessary to resort to hypnosis, or even to personality analysis at the hands of a trained psychotherapist. It is always of prime importance to release the patient from the haunting idea, suggested by his condition, that he may really choke to death in an asthmatic attack. Above all, the physician must never for a moment forget that a calm, deliberate, and reassuring manner for his own part constitutes one of the most important requisites for success. The patient is in need of spiritual guidance; and the physician must remember that the course of suggestion therapy properly begins with the first step he takes into the patient's room, with the first glance, and with the first words addressed to him.

c) HYPOSENSITIZATION

(1) *Specific Methods*

When the sole or principal cause of an asthma is found to be hypersensitiveness to pollen, house or occupational dust, feathers or other inhalants, hyposensitization, either subcutaneously or intracutaneously, often produces satisfactory results. The same applies to cases in which bronchial or skin tests with rusts or molds are positive. Since the principles of hyposensitization and the technic by which it is accomplished are thoroughly discussed in Part One, they need not be repeated here.

In infectious asthma—that is, where the condition first appeared following an acute disease of the respiratory tract (pertussis, influenza, bronchopneumonia), as well as in cases with chronic bronchitis or sinusitis—autogenous vaccine therapy is often very successful. In the former cases, sputum or nasal or pharyngeal secretions are used for preparing the vaccines; in the latter, material aspirated from the bronchi by means of a bronchoscope, or from infected sinuses. Among the bacteria, *Streptococcus hemolyticus* and *Str. viridans* are of the greatest importance; less often, *Micrococcus catarrhalis* and, still

more rarely, Friedlaender's bacilli and pneumococci are found. Especially gratifying results obtained with autogenous bronchoscopic vaccines have been reported by Crump,²⁸⁶ Clerf,²⁸⁷ and others. Many authorities—Stevens,²⁸⁷ for one—use filtrates of cultures of respiratory bacteria, while others advocate a combined vaccine-filtrate. Although it is still an open question whether these methods are specific or nonspecific in nature, many authors, including the present writers, tend to favor the former idea. This view is strongly supported by the fact that fairly large initial doses—for example, 20,000,000 to 50,000,000 organisms—often evoke asthmatic attacks. The argument that good results can also be obtained with stock vaccines does not, in the writers' opinion, militate against the fact of the specificity of vaccine therapy, for specific antibodies are also increased by these vaccines, by a metaspecific mechanism (see p. 28).

Another highly controversial question is as to whether or not the dosage should be based on the outcome of skin tests. Thus, Moody and Howard,²⁸⁸ Stevens,²⁸⁷ and others insist either that they were not able to obtain skin reactions with their preparations, or that the results of the skin tests could not be considered as a guide for treatment. Other clinicians, including the present writers, determine the dosage according to the reactions produced. In the authors' opinion, this wide divergence in views may be explained by the fact that when filtrates are used in the case of individuals hypersensitive to bacteria, the skin tests are almost invariably negative, while tests performed with vaccines, which contain bacterial proteins, almost always elicit positive reactions (see p. 443).

The best results are achieved in cases in which the infection is not of very long standing. Moreover, children seem to respond more favorably than adults, as a rule. It must be remembered that treatment should be continued for a long time, at least for over a year, and must always be resumed on the slightest recurrence. In agreement with Vallery-Radot,²⁸⁹ the present writers prefer the

²⁸⁶ CRUMP, J. *Am J Dis Child* 58: 768, 1939

²⁸⁷ STEVENS, F. A. *J. Pediat* 14, 307, 1939

²⁸⁸ MOODY, E., and HOWARD, W. M. *Arch. Pediat.* 58: 774, 1941.

intracutaneous method, they believe further more, that better results can be achieved with small doses often not exceeding 10 000 to 100,000 organisms, than with the large quantities generally administered

More recently, autogenous oral vaccines have been tried by several authors including the writers, and seem to promise satisfactory results in selected cases. Here again we must sound a warning against beginning treatment with the enormous doses (50,000,000 to 60,000,000 organisms) that the stock preparations contain, we have seen severe asthmatic attacks following such excessive doses. In the writers' own material better therapeutic effects have been obtained with small doses of the preparations diluted 1/10 or 1/100 with lactose depending upon the severity of the case, and administered in gradually and slowly increasing concentrations.

The junior author observed a very satisfactory result obtained with the use of staphylococcus toxoid in one case with *Staphylococcus aureus* in the sputum.

Coke⁸⁰ has suggested injections of autogenous bacteriophage in infectious or microbic bronchial asthma.

Many authors, including Danysz,²⁹⁸¹ Benson,²⁹⁸⁴ and Hajos²⁹⁸³ recommended autogenous stool vaccines when the intestinal flora contains *Str. viridans* or is otherwise abnormal, and report excellent results.

When the specific agent is unknown and there is evidence that the attacks are due to an allergen of auto endogenous origin, injections of the patient's own serum may be administered on the assumption that the allergen is formed within the organism. As an example, we may cite the treatment of premenstrual asthma by means of autogenous blood serum withdrawn in the premenstrual stage. The course usually consists of two or three series of about ten intracutaneous injections of 0.2 cc given every other day (see p. 856). In other cases of endogenous asthma, Jacquelin and Bonnet⁷⁹⁶ inject autogenous serum into the nasal mucosa. The majority of authors prefer autohemotherapy, injecting the whole blood into the buttocks. Lapp²⁹⁸⁶ however, employs autoserotherapy

by the subcutaneous route giving 1.0-1.5 and then successive doses of 2.0 cc of serum for a total of twelve injections.

Herz²³⁷⁹ reported good results in controlling asthma attacks with auto urotherapy. A similar line of reasoning has led the senior author to use the urinary protease method (p. 123) of Ortel and Barber. The initial injection is 0.1 cc of a 1/10 dilution of the lowest concentration to which the patient gives an appreciable skin reaction usually about 1/1,000 or 1/10,000. The injections are given subcutaneously once a week and the dose is increased by 0.1 cc each time. This method was found to be of value in occasional carefully selected cases. Savy and Thiers²³⁷¹ independently came to the same conclusion.

(2) Metaspecific Methods

As stated in some detail on page 211, the writers are of the opinion that the results obtained in allergic diseases by treatment with tuberculin, peptone and similar agents cannot properly be considered as nonspecific in character, but must rather be regarded as metaspecific. That is, the tuberculin for example, results in an increase of specific antibodies by reason of its metantigenic effect. A comparable mechanism is probably the basis of irradiation therapy (X ray, ultraviolet) since it causes protein disintegration in the tissues thereby leading to the formation of metantigens, which, in turn promote the production of specific antibodies. Metaspecific hyposensitization is indicated in those cases of asthma in which the specific agent remains undiscoverable.

Treatment of asthma with tuberculin was introduced by Bouveyron⁷²⁷ and later empirically recommended by van Leeuwen.⁷²⁸ While this method has been widely utilized in Europe, it has scarcely been used in the United States. The writers do not hesitate to declare that when applied to suitable cases, the tuberculin treatment of asthma produces excellent and often long lasting results. However, the following prerequisites must always be remembered: (1) Koch's original old tuberculin (human type) must always be

²³⁷⁹ HERZ K. *Muenchen med. Wchnschr.* 78: 398, 1931.

²³⁷¹ SAVY P. and THIERS H. *Presse med.* 42: 161, 1934.

⁷²⁸ BOUYEYRON A. *Compt. rend. Soc. de biol.* 86: 19, 1922.

employed—investigations are under way to ascertain whether the purified protein derivative of tuberculin has the same therapeutic effect; (2) the dilutions must always be prepared by the physician on the day the injection is to be made*—commercial preparations already diluted are utterly worthless; (3) this type of treatment is suitable only for those patients who respond with a marked delayed local reaction, after twenty-four to forty-eight hours, to a test injection of 0.1 cc of a 1:1,000,000 dilution; (4) patients with active tuberculosis must be rigorously excluded.

Like many other allergic individuals, asthmatics are highly sensitive to tuberculin. Provided that the history, physical examination, and chest X-ray are not indicative of a specific process, this cutaneous reactivity signifies only a slight past tuberculous infection, which the majority of urbanites have experienced. If the cutaneous hypersensitiveness is of a very high degree, treatment must be begun with 0.1 cc. of a 1:10,000,000 and sometimes even of a 1:100,000,000 dilution. The injections should be given subcutaneously. The amount should be increased very slowly, and only if the local reaction is no larger than 1 cm. in diameter, and if no focal or general manifestations appear. When the patient manifests strong reactivity, the dosage is not to be changed. The results obtained are not dependent upon the rapidity with which the individual doses are increased. The maximum should never exceed 1 cc. of a 1:10,000 dilution. At the beginning, the injections are to be given once weekly, then twice monthly, and so on. Treatment is continued for one year, even if the symptoms of asthma have completely disappeared.

Less effective, but frequently quite beneficial, is subcutaneous *peptone* therapy. Witte's peptone (Special XXX) and Armour's peptone are recommended. Treatment is begun with 0.1 cc. of a 0.5 per cent dilution

and doubled twice weekly. The maximal dose is 1 cc. of a 5 per cent concentration. When the intervals between injections are too long, there is a danger of sensitization in the form of strong local and even general reactions. For this reason, the patient should remain under observation for half an hour following each injection. Intravenous injections of peptone, as recommended by Auld, are dangerous in the writers' opinion and should therefore never be undertaken.

Some authors give injections of *milk*. Since severe anaphylactic manifestations following this procedure are not entirely uncommon, we definitely advise against it.

The heterospecific methods also include injection of *stock bacterial vaccines*. The latest addition to the long list of preparations used for this purpose in Sokal's²⁷³ introduction of pertussis vaccine. He recommends subcutaneous administration of 1,000,000,000 organisms of the pure single-strength preparation of Squibb, given once weekly about ten times.

Lastly, mention should also be made here of actino- and roentgenotherapy.

Ultraviolet therapy—never to be administered without first determining that the patient is not unusually sensitive to light—consists of irradiating the whole chest or back with a full erythema dose, with the result that, a few hours later, the area exhibits marked erythema and sometimes even small vesicles, while the temperature may rise slightly. This treatment is given once a week and often brings good results. One must make sure, however, that pulmonary tuberculosis is not present. The Knott technic—the extra-corporeal ultraviolet irradiation of a portion of the blood which is then returned to the patient intravenously—has also been employed. Miley, Seidel, and Christensen²⁷⁴ reported the control of 45 cases of intractable asthma in a series of 56 patients, by means of treatments at intervals of four to six weeks, until some relief was noted, then every eight to ten weeks, and finally only three or four times a year. Our experience with this method, however, was unsatisfactory.

Roentgen irradiation in asthma merits a somewhat more detailed discussion here, since

* The following technic was found to be very convenient and economical. Three rubber-stoppered vials containing 4.95 cc. of sterile normal saline are prepared and pre-labeled 1:100, 1:10,000, and 1:1,000,000 respectively. First, 0.1 cc. is withdrawn from the first vial into a sterile dry tuberculin syringe, followed by 0.05 cc. of the undiluted old tuberculin. The contents of the syringe are then forcefully expelled into the first vial and thoroughly mixed, resulting in a 1:100 dilution. Transfer of 0.05 cc. of this into the next vial gives a 1:10,000 dilution, and a further similar procedure a 1:1,000,000 dilution. Interpolations can be arrived at quite easily.

²⁷³ SOKAL, H. B. *N. Rec.* 155: 437, 1942.

²⁷⁴ MILEY, G. F., SEIDEL, R. E., and CHRISTENSEN, J. A. *Arch. Phys. Therap.* 21: 533, 1943.

this method constitutes a valuable therapeutic adjunct in some cases. As early as 1906, Schilling made the observation that a patient with chronic bronchitis and asthmatic manifestations was relieved of his attacks after a prolonged fluoroscopic examination. Since then, numerous authors have reported favorable results from irradiation of the thorax. However, the technic, and above all the roentgen dosage, are by no means uniform. Maytum and Leddy²³⁷⁵ irradiate one anterior and one posterior field over the mediastinum with 500 r once (5 milliamperes, 6 mm aluminum filter, distance 40 cm, 135 kilovolts). Klewitz²³⁷⁶ chooses four fields on the back and three on the chest (the precordial area is not treated), each measuring 10 by 15 cm, and irradiates one field daily with 150 r (5 milliamperes, 0.5 mm copper plus 1 mm aluminum filter, distance 30 cm, 135 kilovolts). If reactions appear, a day is skipped. After an interval of four weeks, this course of irradiation is repeated, even if the first has been completely successful, a third series of treatments is sometimes given after an interval of three months. In children under 10 years of age, each field, which is proportionately smaller, of course, receives 100 r, with 0.3 mm zinc plus 1 mm aluminum filtration. Hull, Balyeat, and Chont²³⁷⁷ employ a "crossfire" technic in which six fields of the chest (two anterior, two posterior, one of each lateral wall) are irradiated, two fields each receiving about 100 r at one time. Each field is generally irradiated twice during the course of treatment, with a total dose between 800 and 1,600 r. When there is evidence of sinus infection, irradiation of the latter is also carried out. The treatment was of value only in those asthmatic patients with infection either of the bronchi or paranasal sinuses. Kaplan and Rubinfeld²³⁷⁸ reported good results with 100 to 150 r (5 to 20 milliamperes, 0.5 mm copper plus 1 mm aluminum filtration, distance 40 to 50 cm, 200 kilovolts) to both anterior and posterior surfaces of the thorax.

Treatments were given two or three times weekly until a dose of 600 r was administered to each portal, although some patients required up to 1,800 r before relief was obtained. The older and more severe the disease the better was the response. However, there was nearly always recurrence of the attacks.

By means of Klewitz's technic, the senior author has frequently obtained satisfactory and long lasting results. It must be expressly noted, however, that there is no such thing as a generally applicable rule for the doses to be given at each irradiation. It may be said that the more severe and more frequent the attacks, the smaller should be the initial doses (sometimes no more than 50 r), and the longer the intervals between irradiations (from one to seven days). A second series is administered four or five weeks later, but only if marked improvement can be observed following the first. Then, when there are only occasional attacks or slight symptoms, the intervals may be considerably prolonged for example, possibly only one field is irradiated per week, with the result that a series performed in this manner may last as long as seven weeks. It cannot be denied, however, that occasionally a marked exacerbation of the asthmatic condition occurs after the very first irradiation, if this happens, the treatment is of course immediately stopped. This type of response has been observed chiefly in tuberculo allergic asthma. Moreover, the unpleasant manifestations of X ray sickness are not uncommon, they can be readily controlled, however, by the administration of vitamin B₁ injections, or vitamin B complex, or liver extract along with a sedative, such as sodium pentobarbital (nembutal) by mouth. Despite these possible disadvantages, we recommend that roentgen treatment be tried—with all due caution—in severe and chronic cases of bronchitis asthma, if other therapy is unsatisfactory. It should be stressed, in this connection, that the sooner irradiation is undertaken, the better the results are likely to be.

In 1920 Groedel, Drey, and Lossen made the accidental observation that splenic irradiation, in the case of a patient with leucemia as well as asthma of many years' duration, resulted in an appreciable diminution in the severity and

²³⁷⁵ MAYTUM C. K. and LEDDY E. T. *J. Allergy* 10: 135, 1939.

²³⁷⁶ KLEWITZ F. *Med. Welt* 8: 580, 1934.

²³⁷⁷ HULL W. M., BALLEAT R. M. and CHONT L. K. *Am. J. Roentgenol.* 49: 227, 1943. *J. Allergy* 15: 155, 1944.

²³⁷⁸ KAPLAN I. I. and RUBINFELD S. *Am. J. Roentgenol.* 50: 791, 1943.

frequency of the asthmatic attacks. Ever since, irradiation of the spleen has not infrequently brought good results (technic: frontal and lateral portal, 10 by 15 cm., each treated twice with 100 to 150 r, with 0.5 mm. copper and 1 mm. aluminum filtration, at a distance of 40 cm.)

Many authors expose both the lungs and the spleen. In addition to the spleen, the thyroid, the pituitary gland, or the liver is also irradiated by some.

Zuppa²³⁷⁹ treats the perirenal area with 100 to 150 r, at twenty-day intervals, on a field of 10 by 15 cm., between the eleventh and thirteenth thoracic vertebrae; about ten treatments are given. The aim of this approach is to stimulate the adrenals to increased activity. Zuppa bases this treatment on the concept that there is a sympathetic imbalance in asthma, as a result of which adrenal hormone production becomes inadequate.

Furthermore, similar good results have been reported following irradiation with Bucky's grenz rays and following short-wave therapy.

It is not, as yet, fully understood just how such therapy exerts its beneficial effects. As mentioned above, many authors assume that irradiation of the hilum of the lung, where most enlarged lymph nodes are located, serves to release quantities of altered tissue products. This is surely the case in irradiation of the spleen and liver. Moreover, it may be said that the factor of suggestion probably plays a part in those cases in which the very first treatment brings relief. Other authors interpret the beneficial effect as the result of the influence of roentgen rays on the overexcited nervous system. Lastly, the opinion has been advanced that X-rays decrease the secretory activity of the mucous glands of the bronchi.

d) DEALLERGIZATION

Of the various methods of deallergization mentioned on page 212, the oral approach is the only one that requires consideration. When a food, pollen, or drug is known to be the cause of the condition, excellent and long-lasting results may be achieved by administering slowly increasing doses of minute quantities of the allergen. Similarly, oral

deallergization with autogenous dust extract is well worth trying (p 238). Also to be mentioned here are the skeptophylactic methods—that is, administration of small quantities of the given food or drug prior to ingestion of larger amounts of the same substance. Finally—and based on the same principle—there is the propeptan method (p 217), with which Urbach,²³¹⁸ Ulrich,²³²⁰ Woita,²³²¹ and others have achieved good results.

e) MANAGEMENT OF ASSOCIATED CONDITIONS

Cardiopathy

The importance of the cardiac component in asthma was discussed at some length in the relevant section. Here it should be stressed once again that, with the earliest clinical indications of involvement of the heart, or even in their absence in severe status asthmaticus as well as in prolonged chronic asthma, appropriate cardiac therapy should always be instituted. The most suitable method consists in administering small doses of digitalis (0.1 Gm., or 1½ grains) once or twice daily, preferably in combination with ephedrine, caffeine, phenobarbital, and aminophylline (see prescription on p 651). In exhausting attacks, the intravenous injection of strophanthin (0.25 to 0.5 mg. or 1/240 to 1/120 grain) will be far more helpful. This drug is best administered in combination with aminophylline and dextrose.

	Gm. or Gc.
B; Strophanthin K (Abbott)	0.00025
Aminophylline	0.24-0.48
10 per cent glucose	q s ad 10

The only contra-indication to the use of strophanthin is previous digitalization. When it is necessary to employ this drug in the case of a patient who has previously received digitalis, and if a rest period of two or three days cannot be allowed, small doses of strophanthin (0.15 mg., or 1/400 grain) may be injected very slowly, while the patient is carefully observed for extrasystoles. These, or the appearance of pulsus bigeminus, are indications of strophanthin intolerance and call for administration of quinidine sulfate,

²³⁷⁹ ZUPPA, A.: Arch. di radiol. 9 1117, 1935.

²³¹⁸ URBACH, G. R. Ugeskr. f. Læger 95 365, 1933.

²³²¹ WOITA, H. Therap. d. Gegenwart 78 53, 120, 1937.

which will depress the hyperexcited centers (Pick²³⁵⁷)

Rhinopathy

Proper management of the nose and paranasal sinuses, provided these are involved, plays an important part in the treatment of asthma. As explained in some detail on page 600, rhinopathy and asthma are produced, in a high percentage of cases, by the same agent (infectant or nonbacterial allergen). This does not exclude the fact that nasal involvement quite frequently precedes the asthmatic symptoms. Indeed, the latter would often be prevented if the former could be controlled in time. This is particularly true in children.

From reports in the recent literature and on the basis of their own experience, the present writers have concluded that the treatment of the sinuses should be primarily conservative. Allergic study and treatment should be instituted and continued for a sufficient period of time to determine whether satisfactory results can be obtained by this means. The conservative measures to be employed depend largely on the decision as to whether an infectious or a nonbacterial allergy is responsible for the nasal and paranasal symptoms. In the former case, good results will often be achieved by means of local treatment with penicillin instillation (1,000 units per cc of paterdrine), with a sulfonamide solution or suspension in the Parkinon head-low position or by displacement technics, with the use of luminous infra red irradiation to the head to liquefy the secretions, with roentgen therapy (see p 507), and with autogenous vaccines. In addition, the application of vasoconstrictors gives temporary relief. A purulent sinus infection naturally calls for thorough local drainage. Operations are to be performed only when the sinus disease itself presents indications for surgical intervention. Even such a drastic operation as Caldwell Luc's will not, according to Schenck and Kern,²³⁵⁸ afford permanent cure of a sinus infection. These authors showed that in about one third of their surgically treated cases freedom from symptoms lasted only from three to seven months, in half of the

patients operated on, the old manifestations reappeared after about two years, and in 17 per cent, surgical intervention brought no relief whatsoever.

Polyps should be removed only if they are composed of fibrous tissue. Submucous resection is indicated solely if there is definite obstruction. Turbinectomy should be avoided, if possible, since, following this operation, the air reaching the bronchial tree may be too cool and therefore tend to cause exacerbation of the asthma.

From the discussion above it will be seen that it is of the greatest importance in the patient's interest for the allergist and the rhinologist to collaborate closely.

Bronchitis

In view of the pre eminent importance of bronchitis as a factor in eliciting asthmatic attacks, either as the direct cause of a bacterial allergy or by reason of the mechanical irritation of the bronchial mucosa resulting from the severe cough, the necessity for treating this condition cannot be too emphatically stressed.

The principal and most distressing symptom of bronchitis is the persistent mucosal irritation leading to coughing spells. Depending on the cause of the bronchitis and its stage, the nature of the cough varies and accordingly requires different therapeutic measures. Four rather distinct types may be recognized (Brown²³⁵⁹): (1) the hacking, irritating unproductive cough that occurs in the early congestive stage of acute tracheitis and bronchitis, (2) the "tight" cough, with scanty and tenacious sputum, encountered at the onset of an asthmatic attack, (3) the wheezy squeaking cough found at the end of asthmatic seizures, and (4) the loose cough with abundant sputum. The art and science of prescribing appropriate expectorants requires correct appraisal of the type of the cough and the character of the sputum. An expectorant may act as a stimulant, sedative, or anodyne. The stimulating expectorants are intended to irritate the mucous membranes in such a manner as to stimulate repair. Typical of this group are terpin hydrate (0.2 to 0.3 Gm., or 3 to 5 grains, three times a day) and creosote (calcreose, 0.25 Gm., or 4 grains, three times daily).

²³⁵⁷ PICK E. P. *J Mt Sinai Hosp* 7: 181, 1940.

²³⁵⁸ SCHENCK H. P. and KERN R. A. *J Allergy* 3: 296, 1932.

²³⁵⁹ BROWN C. L. *JAMA* 109: 268, 1937.

The sedative expectorants have a soothing action on the acute inflammation, mainly in that they increase the secretion of protective mucus. They may be demulcents, as acacia (4 cc., or 1 dram of the syrup) or glycyrrhiza (in the same dose); nauseants, as ipecac (0.3 to 0.6 cc., or 5 to 10 minims of the syrup); salines, as ammonium chloride (0.6 to 1 Gm., or 10 to 15 grains); and alkalies, as ammonium carbonate (in the same dosage). Anodyne expectorants are employed to depress the excessive cough reflex. They usually diminish secretion. Codeine is the chief representative of this group (0.02 to 0.03 Gm., or $\frac{1}{2}$ to $\frac{1}{2}$ grain, two or three times a day, as necessary). It should be employed with caution in severe asthma. Small children usually tolerate codeine well, and even infants may safely be given 0.005 Gm. (1/12 grain) of codeine a few times daily.

In practice, the various medications are advantageously combined, according to the patient's needs.

When the cough is tight and the sputum scanty, as in acute bronchitis, the following mixture is often helpful:

	Gm. or Cc	
R Ammonium chloride	10	℥ss
Elux of glycyrrhiza	60	℥ss
Syrup of acacia	q s ad 120	℥iv

M.Sig.: 1 tablespoonful in half a glass of water every two hours

If the patient objects to the taste of ammonium chloride, or if it produces nausea, administration in the form of enteric-coated tablets is usually well tolerated.

For the wheezy cough, one may employ:

	Gm. or Cc	
R Potassium iodide	15	℥iv
Tincture of stramonium	20	℥v
Syrup of iolu	q s ad 120	℥iv

M.Sig.: 1 teaspoonful three times a day, after meals, best with hot milk.

In cases with distressing cough, the following mixture may be recommended for adults:

	Gm. or Cc	
R Ammonium iodide	4 0	℥i
Aromatic spirit of ammonia	2 0	℥ss
Camphorated tincture of opium (Ephedrine sulfate)	3 0	℥ss
Fluid extract of glycyrrhiza	(0 3)	(gr v)
Water	12.0	℥ss
	q. s. ad 180.0	℥vi

M.Sig.: 1 tablespoonful three times a day.

For children, the following may be used:

	Gm. or Cc	
R Codeine sulfate	0 25	gr v
Ephedrine sulfate	0 36	gr vi
Tincture of belladonna		
Tincture of lobelia	ad 4 00	℥ss
Potassium iodide	8 00	℥ss
Elux of terpin hydrate	q s ad 120 0	℥iv

M.Sig.: 1 teaspoonful three times a day

In addition to oral medication, inhalation of steam is highly recommended. Where available, carbon dioxide inhalation is the most efficient of all expectorants, and is advocated by Holinger et al²³⁵ in any instance where bronchial obstruction is a prominent feature of the attack, or when there is accumulation or retention of inflammatory exudate in the bronchial tree. Banyai and Cadden²³⁶ confirmed the efficacy and safety of this method, employing a mixture of 10 per cent carbon dioxide and 90 per cent oxygen for five to fifteen minutes, one to three times daily, administered by means of a mask or a glass tube.

Since attacks at night and in the early morning are very frequently caused by the drying out of the mucous membranes of the lower respiratory passages, the air in the patient's bedroom should be kept humid and warm during the night. For this purpose, a vaporizer may be used; or large linen cloths, soaked in hot water, may be hung up near the bed, and hot wet packs may be wrapped around the patient's chest and throat. Preferable to this is the use of oil compresses on the chest; a Turkish towel, soaked in hot olive or salad oil, is wrapped around the patient's throat and chest, and is then covered with oiled silk over which hot water bottles are placed. Relief is also frequently obtained by drinking hot liquids, such as a cup of hot milk containing melted butter and honey.

Similar results can be achieved with mustard plasters, radiant heat light, or short wave diathermy to the chest. The latter method relieves the pain and discomfort in the chest, reduces the viscosity of the secretions, and thus makes expectoration easier.

²³⁵ HOLINGER, P., BASCH, F. P., and PONCHER, H. G. *ibid* 117, 675, 1941

²³⁶ BANYAI, A. L., and CADDEN, A. A. *Am J M Sc* 206 479, 1943, *Brit J Tuberc* 38, 111, 1944

The following simple instructions to the patient are of great importance. He must be instructed to cough not with wide-open mouth or unrestrainedly, but with a minimum of moderate effort as though he were merely trying to clear his throat. The patient often has a faulty breathing technic, which must be corrected without fail. He should be taught to breathe through his nose, particularly when out in the cold, in order to warm and moisten the inhaled air.

Treatment by means of the pneumatic chamber is discussed on page 655.

In suppurative types, adequate doses of one of the sulfonamides, intramuscular injections of penicillin, or inhalation of penicillin aerosol often produce amazingly good results, provided the causative organism is sensitive to the drug. However, the effects are not usually lasting. Hence these methods are best employed for the control of acute exacerbations or in the initial phase of treatment.

When the bronchitis has been overcome, the physician is confronted with the problem of hardening the patient to exposure to cold. This is best accomplished by systematic increasingly colder applications or showers, as well as by breathing exercises (see p. 654).

When bronchiectasis complicates asthma, it should be treated, in addition to a careful antiallergic regimen, by general hygienic measures: postural drainage over a long period of time, repeated bronchoscopic drainage, and when indicated, by lobectomy. General hygienic measures include adequate diet and rest, administration of vitamins, and removal of definite foci of infection, especially in the paranasal sinuses. The expectorants and inhalants mentioned above are used as adjuvants.

According to Thomas et al.,²³⁸⁷ all cases of bronchiectasis which are nonsurgical should, unless otherwise indicated, be given an adequate trial of sulfonamide therapy. When allergy of the respiratory tract is a complicating or etiologic factor, as occurred in about one-half their cases, appropriate measures should be instituted—avoidance of environmental allergens, dietary restrictions, hyposensitization therapy, and administration of autogenous

vaccine depending on findings in the individual case. A combination of these two approaches, along with postural drainage in some cases appeared to produce the best therapeutic results. Recurrences were frequently noted following acute respiratory infections, cessation of allergy management, or sometimes when the courses of sulfonamide were in adequate. The effects of penicillin have been generally disappointing (Stookey et al.²³⁸⁸) and those of penicillin aerosol require further evaluation, although preliminary observations have been encouraging (Olson^{2389a}).

Tuberculosis

In the treatment of tuberculo-allergic asthma, it is first necessary to determine whether the condition is still monospecific or whether it has already become pathergic (as had occurred in about one half of our cases). In the strictly tuberculo-asthmatic cases, the writers recommend, as most beneficial, subcutaneous tuberculin therapy, administered with extreme caution and over a long period of time. It is best to begin with 0.1 cc of a 1:1,000,000,000 dilution of old tuberculin, and then to increase the strength of the doses gradually. It should be especially noted that cardiac therapy is essential; digitalis and even strophanthin and glucose injections are recommended. If the disease has already become pathergic—i.e., nonspecific—a course of tuberculin treatment should be instituted, in addition to other treatment for pathergic asthma.

f) CONSTITUTIONAL THERAPY

Any number of approaches and methods may be properly included here, such as venesection, application of leeches, laxatives, diuretics, counterirritation, fever therapy, and radical changes in diet, any of which may be found to be helpful—for reasons as yet unknown—sometimes even in severe and apparently intractable cases of nonspecific asthma. Here too one must consider, of course, the possibility of psychogenic influences. Moreover, it has long been appreciated that the asthmatic condition is often relieved by severe infections

²³⁸⁷ THOMAS J. W., ORDSTRAND H. S., VAN and TOMLINSON C.
Ann. Int. Med. 23: 405, 1945

²³⁸⁸ STOOKEY P. F., LOCKWOOD I. H., MANTZ I. L., BUCKINGHAM W. W., UPSHUR A. E., and HERRARD B. South. M. J. 38: 98, 1945

^{2389a} OLSEN A. M. Proc. Staff Meet. Mayo Clin. 20: 154, 1945

accompanied by fever (e.g., pneumonia or erysipelas), by surgical operations of almost any kind, by accidents, and by starvation. What all these factors have in common is that they bring about a radical change in the patient's organism—something that cannot be properly put into words—the untranslatable *Umstimmung* of German medicine. It is interesting to note that these remedies were widely used in the Middle Ages, and in China even long before the time of Christ.

Rackemann²¹⁹⁶ has stressed the importance of the treatment of "depletion" in chronic asthma, along with "allergic cleanliness." Steps should be taken to improve the general hygiene by regulating the time and quality of meals and daily activities, ensuring adequate rest periods, fresh air, outdoor exercise, and also extra vitamins and vaccines in most cases. Many of these patients need treatment more for their general condition than on the basis of allergy.

Vomiting

In severe cases of asthma, the patient may be given:

	Gm. or Cc	
R̄ Ipecac	1 3	gr xx
Tartar emetic	0 12	gr ii
Oxymel of squill	q s ad 60 0	3 ii

Sig.: 1 teaspoonful every fifteen minutes until the patient has vomited three times

Vomiting can also be induced by subcutaneous injection of 5 to 10 mg. ($\frac{1}{2}$ to $\frac{1}{8}$ grain) of apomorphine.

Infants and young children may be given a teaspoonful of oxymel of squill with some camomile tea every quarter hour until vomiting begins. The following may be advantageously administered to older children: wine of antimony, 5 to 30 drops, every quarter hour till effective.

Laxatives

Strong purgation is also often beneficial. For this purpose, magnesium sulfate (2 tablespoonfuls dissolved in warm water) or castor oil (1 or 2 tablespoonfuls) may be given once or twice daily until drastic result is obtained. In severe cases, calomel (0.2 Gm., or 3 grains) may be taken for a few days,

provided the patient is not hypersensitive to mercury.

Diuretics

Theobromine sodiosalicylate (diuretin) (1 Gm. or 15 grains a day), or aminophylline (0.1 to 0.2 Gm., or $\frac{1}{2}$ to 3 grains) in tablets and in double the dose in rectal suppositories, or solution of potassium acetate ($\frac{1}{2}$ to 1 teaspoonful in a half glass of water, several times a day) is sometimes of value.

Vesiculation and Related Methods

The Chinese have employed the method of acupuncture since time immemorial. One or more needles are introduced into the sternum at the level of the nipple line and allowed to remain there for a few minutes. In severe cases, the "fontanelle" method may be tried. A blister is produced by means of a cantharides plaster, and healing of the subsequent lesion is prevented for several days by the daily application of an ointment containing cantharides. The fontanelle must be carefully bandaged to prevent the lesion from drying out. In especially severe cases it may be advisable to produce a sterile abscess by means of injection of sterile turpentine, or to use the *point de feu* technic of the French, in which small superficial burns are produced in the skin by means of a hot cautery. As a last resort, the heroic method of A. Bier can be tried, it consists in deep burning of the skin of a palm-sized area on the thigh to the stage of carbonization. The senior author employed the last-mentioned approach in 2 cases of intractable asthma of many years' duration, in one with fairly good results.

Fever

Most suitable for this purpose is a preparation known as pyriker, a bacterial vaccine of specially selected organisms, in different strengths. According to Klewitz,²²⁷⁶ 0.4 cc. of the no. 1 strength is given for the first dose; for children the dosage is correspondingly smaller. Despite the high fever, the subjective complaints are not severe. The second injection is given three or four days later; if the first dose elicited a strong reaction, it will be unnecessary to increase the dose for the second injection. The senior author has some-

times obtained excellent results with pyrif, and even uses this method in cases complicated by myocarditis, along with appropriate cardio therapy

Other authors prefer typhoid or *Bacillus coli* vaccine for inducing fever. Jimenez Diaz²³² also advocates injection of a suspension of sulfur in oil for this purpose

Feinberg²³⁴ and Phillips²³⁵ recommended hyperpyrexia by diathermy or high frequency currents

The interesting experimental work of Stoesser and Cook²³¹ sheds some light on the mechanism of fever therapy. These authors reported excellent results in children when the diet was kept low in salt (less than 200 mg daily). Relief was only transient however, if the salt intake prior to or during the fever treatments was normal or high. The authors also found that remissions due to artificial fever plus low salt intake could be promptly terminated by the addition of 1 or 2 Gm of sodium chloride to the diet

Diet

It has long been known that starvation or deliberate undernourishment definitely tends to alleviate asthmatic attacks and sometimes even to prevent their appearance. Within the past few years, these old therapeutic measures have to a certain extent again come into favor. Rackemann²⁰ recommends that in severe cases food be withheld for twenty four to forty eight hours but that fluids with the exception of milk be forced. Schilling²³⁶ prescribed rest in bed, a diet consisting only of fruit juices for several days, together with 1 or 2 tablespoonfuls of magnesium sulfate, light cabinet treatments and supportive measures for the heart. Bottenberg²³⁸ reports a case of severe asthma that was cured by a fasting diet of twenty six days' duration followed by five bouts of pyrif-induced fever. Fasting is certainly the most drastic curative measure—the conservative knife," so to speak. The present writers have also had success with

strict raw fruit and raw vegetable diets for a few days at a time

The organism's fluid balance is disturbed by the asthma attack. Long ago the French clinicians called attention to the flood of urine following attacks and coined the descriptive term *urina spastica*. More recently it has been determined by means of accurate methods, that the body has a tendency to store water in the period preceding the attack. It is assumed that these processes are regulated from some center located in the midbrain. According to Marx,²³⁹ they can be influenced by means of a dehydrating and salt free diet. He prescribes the following for two or three days, nothing but fruit without any additional liquids, then a few days on raw fruit and vegetables which still constitute an inadequate caloric intake. Thereafter beginning with the fifth day, the patient is put on a salt freedry diet. Protein is not restricted 100 to 200 Gm of meat per day being permitted but spices are forbidden. Moreover, for some time only raw foods are allowed for one or two days a week. Cooke¹⁰⁸ advocates dehydration by means of a low salt diet, or a low sodium acid ash diet, often in combination with a potassium salt of iodine or chlorine. Patients with severe asthma are placed on fluids, weak tea, fruit or vegetable juices without salt and given vigorous catharsis by means of compound cathartic pills and magnesium sulfate, followed by an enema or colonic irrigation.

On the basis of the concept that asthma is associated with hyperinsulinism Abrahamson²⁷ has employed a low carbohydrate high fat diet with the food divided into frequent small meals. This is not far removed from Peshkin and Fineman's²³⁹ low carbohydrate, ketogenic diet for asthmatic children.

Some authors were of the opinion that asthmatic attacks cause a shift of the acid base equilibrium to the alkaline side and that the success of starvation diets could be attributed to the resulting acidosis. They recommend, therefore, an acid diet with added ammonium chloride. On the basis of his investigation of 1,500 cases however, Adam²³⁹ was unable to confirm the presence of alkalosis.

²³² JIMENEZ DIAZ C. *Schweiz med Wchnschr* 72 20 1942

²³³ PHILLIPS A. *Arch Phys Therapy* 17 282 1936

²³⁴ STOEßER A. V. and COOK M. M. *Am J Dis Child* 60 1252 1940

²³⁵ SCHILLING E. *Ztschr f aerztl Fortbild* 31 226 1937

²³⁶ BOTTEBERG H. *Hippokrat* 1937 p 1113

²³⁷ MARX H. *Fortschr d Therap* 12 461 1936

²³⁸ PESHKIN A. M. and FINEMAN A. H. *Am J Dis Child* 39 1210 1930

²³⁹ ADAM J. *Br J Med* 1 973 1932

g) SYMPTOMATIC THERAPY

This section is subdivided into discussion of the methods employing drugs, physiotherapy, and the surgical approach

(1) *Drugs*

The drugs usually given in the treatment of asthma are intended to quiet the cerebrum and the brain stem; to relieve the spasms of the bronchial musculature by acting either on the peripheral portion of the autonomic nervous system or directly on the smooth muscle; to inhibit secretion by the glands of the bronchial mucosa; and, finally, to promote expectoration.

In view of the diversity of the aims of medication in asthma, it is obvious that no one drug can meet all the requirements, therefore, several drugs are usually given simultaneously, either in combination or alternately.

Epinephrine and its substitutes, ephedrine, paredrine, neosynephrin, and nethamine are chiefly used to stimulate the sympathetic nerve endings, while atropine, extract of belladonna, and bellafolin are employed for their depressant effect on the terminations of the vagus in the bronchial musculature.

Since these preparations have been described in Part One and in the section on the treatment of asthmatic attacks, little more need be said about their action here. We shall merely present a few prescriptions in which some of the most efficacious drugs are used in combination.

In cases of severe asthma, the present writers recommend the addition of small doses of digitalis to the ephedrine mixtures, even when no myocardial damage is demonstrable.

	Gm.	
R Ephedrine sulfate	0 01	gr $\frac{1}{4}$
Caffeine sodiobenzoate	0 2	gr. $\frac{1}{2}$
(Digitalis)	(0 1)	(gr $\frac{1}{16}$)
Extract of belladonna	0.01	gr. $\frac{1}{16}$
Phenobarbital	0 015	gr $\frac{1}{4}$
Aminophylline	0 1	gr iss

Theobromine sodium salicylate 0.15 Gm. ($2\frac{1}{2}$ gr.) may be substituted for the aminophylline. This combination is given once daily, in the evening, for three consecutive days each week; while the same mixture without the digitalis is given in the morning and at noon. On the remaining four days of the week, the latter preparation only is given two or three times a day. To avoid any

possible confusion, it is advisable to dispense the digitalis-containing mixture in a red capsule, and the digitalis-free one in a white capsule. For patients who usually suffer their attacks after midnight, enteric coated preparations are recommended, such as Enseals of ephedrine and sodium secenal (Lilly), or Luasmin (Brewer and Company), which contains ephedrine, phenobarbital, and theophylline sodium acetate.

The value of aminophylline (theophylline ethylenediamine) was discussed in some detail on page 631. If aminophylline is not well tolerated when taken by mouth, and intravenous administration is not feasible, the rectal route may be advantageously used.

	Gm.	
R Aminophylline	0.50	gr vuss
Benzocaine	0 13	gr ii
Cacao butter q s		suppositoria

Sig 1 rectal suppository once or twice a day

Dees²²⁷ confirmed the effectiveness of aminophylline suppositories and found them to be largely preferred to other methods for attaining symptomatic relief in the patients' opinions. They have been made available commercially (Aminet suppositories—Bischoff). Barach²²⁸ has pointed out that 0.5 Gm. ($7\frac{1}{2}$ gr.) of aminophylline dissolved in 20 cc. of tap water may be instilled rectally by means of a syringe and rubber catheter by the patient or relatives without difficulty. In the opinion of the present writers, this of one of the most efficacious symptomatic methods in controlling asthmatic attacks.

Iodine is one of the most important drugs in the treatment of chronic asthma. Iodine promotes increased exudation by the glands of the respiratory mucous membranes. Since the coughing spells in asthma are frequently the result of dryness of the mucosa of the lower respiratory passages, it is clear that the correction of this can help to eliminate the cough that is often the forerunner and even the elicitor of the attack. However, since there is always some danger of encountering hypersensitivity, giving rise to "iodine coryza" or iodine acne, treatment should always be initiated with small doses—for example, 5 drops of the following mixture, which may be increased

²²⁷ DEES, S. C. *J. Allergy* 14 492, 1943.

after a few days to the same dose three times a day, and finally to 15 drops

	Gm. or Cc	
R Potassium iodide	30 0	3i
Distilled water	30 0	f3i

Sig 5 to 15 drops in water or milk three times a day after meals as directed

Apomorphine in conjunction with iodide has been found useful in reducing the sticky consistency of the mucus in asthma

	Gm. or Cc	
R Apomorphine hydrochloride	0 13	gr ss
Potassium iodide	20 0	3v
Syrup of cherry	qs ad 120 0	f3iv

M Sig 1 teaspoonful every four hours

A combination of iodine and arsenic therapy is also widely used and has frequently given good results when administered in courses of several weeks duration (Kaemmerer³⁰⁸)

	Cc	
R Solution of potassium arsenite	9 0	f5 i
Tincture of gentian	1 0	RRXV

M Sig 3 drops twice a day

	Gm	
R Potassium iodide	12 0	3i
Sodium iodide	4 0	3i
Div pillul no xxx		

M Sig 2 pills twice a day

Because of the irritating effect of iodides on the gastric mucosa they should not be taken on an empty stomach but preferably during or following ingestion of some fat containing food such as milk

The present writers particularly favor the intravenous route of administration for iodides (10 cc of a 10 per cent solution twice weekly) We prefer the sodium to the potassium preparations for intravenous use Ramirez³⁰⁹ gives as much as 250 cc of a 4 per cent solution—10 Gm of sodium iodide—once or twice a week and has reported very good results

Iodides can often be given over a long period of time with absolute impunity However, the physician should always keep the patient under close observation since hyperthyroidism and other severe disturbances occasionally appear Bechet³⁶¹ pointed out that previous ingestion of iodized salt may sensitize the patient to the point that less than the medicinal

doses of iodides may cause severe iododermas and possibly even death The present writers know of a case in which the patient took iodide for years renewing the prescription without medical supervision and lost 48 Kg (105 6 pounds) Iodized poppyseed oil in doses of 5 to 10 cc intratracheally was recommended for a while because marked improvement in the asthmatic condition was noted following the instillation of this oil for diagnostic bronchographic purposes However Crip and Hampsey³⁰⁸ most emphatically warn against this method of treatment since many untoward reactions such as pneumonia acute pulmonary collapse sudden circulatory failure and even immediate collapse and death have been observed Seibold³⁰⁹ found that the mortality rate of asthmatics increased 500 per cent in a twelve month period following the beginning of the use of iodized oil as a therapeutic measure

Niacin (nicotinic acid not the amide) in intravenous doses of 50 to 100 mg two or three times a day was found by Melton³⁰⁵ to reduce the frequency and severity of the paroxysms Treatment is maintained by oral administration of similar doses

Sulfur therapy has occasionally produced good results in asthma It should be noted however that only the colloidal preparations may be injected intramuscularly otherwise local pain prevents continuation of treatment

Potassium nitrate and stramonium leaves are the chief ingredients of asthma cigarettes and of smoke paper (charta potassii nitratis) The vapors which contain nitrites and atropine (the active principle of stramonium) exert a temporary bronchodilating effect provided this method is not used too long or too frequently

	Gm	
R Potassium nitrate	40 0	3x
Powdered stramonium leaves		
Lobelia	30 0	3i

Sig Ignite small portion of mixture and inhale fumes

Sulfonamides can be tried in cases in which the asthma depends in whole or in part, on the presence of bronchial infection (Weil and Climo³⁶⁰) The efficacy of this treatment in

³⁰⁸ CRIP, L. H. and HAMPSEY, J. W. J. Allergy 9 239 1937

³⁰⁹ SEIBOLD, G. J. Texas State J. Med. 36 386 1940

³⁶⁰ WEIL, C. A. and CLIMO, H. J. South. M. J. 34 838 1941

selected cases has been repeatedly confirmed. Penicillin injections and particularly penicillin aerosol serve a similar purpose.

Histamine therapy was first tried in asthma by Ramirez.²⁴⁰¹ But satisfactory results were not obtained until Dzsini²⁴⁴ and Farmer²⁴⁶ introduced the use of very small quantities. Girling²⁴⁷ has claimed excellent responses in 5 of 6 cases so treated. The initial dose is 0.01 to 0.001 mg. in mild cases, and 0.0001 mg. in more severe asthma. The injections are increased each time by 50 per cent if well tolerated; in the beginning they are given two or three times weekly, and later are spaced at five-, seven-, ten-, fourteen-, and twenty-one-day intervals. The rapidity with which the dose is increased, and the spacing of the injections, depend upon the patient's tolerance and the results achieved (For further information, see p. 228).

Histamine-azoprotein complex (Hapamine) has been employed with favorable results by Derbes,²⁴¹ but the potential dangers of this treatment (see p. 229) should be carefully considered.

Pitressin in conjunction with a strict low salt diet has been used by Stoesser²⁴⁹ in cases of chronic asthma in which other methods failed. After seven to ten days of the diet, and provided the weight has been constant for approximately three days, hypodermic injections of pitressin are given every three hours day and night in doses of 0.3 cc. for children and 0.5 cc. for adults. If emesis ensues, the dosage is reduced. Treatment is continued for twenty-four to forty-eight hours or until the patient has gained from 2 to 5 per cent in weight, and the pitressin suddenly discontinued. If the subsequent diuresis is marked, there is improvement in many cases, even though mineral studies indicate a lack of consistency in the excretion of sodium and chloride (Stoesser and Booth²⁴⁰⁴). If there is no improvement, an even stricter salt-free diet is continued for one week, and the treatment repeated.

Insulin shock for the treatment of asthma was first tried by Wegierko,²⁴⁰⁵ and Vollmer²⁴⁰⁶ has confirmed the fact that satisfactory results can be achieved by this method. The effect is ascribed to the formation of adrenalin in the patient's system and to a possible compensatory hyperfunction of the adrenal gland in response to repeated injections. Up to 40 units are given, but in no instance is the hypoglycemic reaction permitted to become severe. After twenty to thirty minutes, the hypoglycemia is carefully controlled by glucose given orally or, if necessary, intravenously. Some fifteen to twenty shocks are required, depending on the severity of the case.

Liver therapy, chiefly by intramuscular injections of liver extract, was first described by Moll,²⁴⁰⁷ and has since been successfully used by Slauck, Delbanco, and others. Nothing definite is as yet known as to how and why this treatment exerts a beneficial effect. In seeking an explanation it might be assumed that, on the one hand, peptone or histamine-like substances play a part, or one might recall on the other hand, that liver extracts contain adrenalin-like substances.

Injections of *testosterone* have been found beneficial in some cases (Ryan and Thomas,²⁴⁰⁸ LaFitte and Guttieres,²⁴⁰⁹ Rackemann²¹⁹⁶). Its mode of action is not clear and further experience is necessary.

Sedatives play a prominent part in the treatment of asthma. Small doses of phenobarbital (0.008 to 0.015 Gm., or $\frac{1}{8}$ to $\frac{1}{4}$ grain) should be given the patient three times a day over a long period of time in order to minimize his anxiety and apprehension. In cases in which the clinical picture is dominated by nervous disturbances, Bellergal ($\frac{1}{2}$ to 1 tablet, 3 times a day) is especially recommended because of its quieting effect on the autonomic nervous system. This preparation contains gynergen, bellafolin, and phenobarbital. The senior author's own good results with this drug were reported by Bauer.²⁴¹⁰

For children in whom asthma was brought

²⁴⁰¹ RAMIREZ, M. A. and GEORGE, A. V. S. M. J. & Rec. 119: 51, 1924.

²⁴⁰² GIRLING, W. N. M.: Northwest Med 42: 196, 1943.

²⁴⁰³ STOEßER, A. V. Letters, Internat. Cong. Club of Allergy, Series 8 1949, 1941, Southwest Allergy Forum, New Orleans, April 1945.

²⁴⁰⁴ STOEßER, A. V., and BOOTH, M. J. Allergy 16: 232, 1945.

²⁴⁰⁵ WEGIERKO, J. Presse méd. 43, 1379, 1935.

²⁴⁰⁶ VOLLMER, H. Arch. Pediat. 56, 223, 1939.

²⁴⁰⁷ MOLL, H. H. Brit. M. J. 1: 916, 1932.

²⁴⁰⁸ RYAN, E. J., and THOMAS, J. W. in Allergy in Clinical Practice Philadelphia: Lippincott, 1941.

²⁴⁰⁹ LAFITTE, A., and GUTTIÈRES, J. Bull. méd., Paris 54: 284, 1940.

²⁴¹⁰ BAUER, H. Schweiz. med. Wchnschr. 65, 178, 1935.

on by emotional upsets or other psychogenic factors, Shulman²⁴¹ successfully employed phenytoin sodium (dilantin sodium) both for its psychosomatic effect and for controlling the attacks. Dosage should be individually determined for each patient. The average was found to be from 0.03 Gm twice a day to 0.1 Gm three times a day. Therapy is continued for periods varying from five months to one year.

(2) *Climatotherapy*

A change of climate is of lasting benefit only in the two types of asthma referred to below, and the beneficial effect endures only if the first type of patient can stay in the new environment for the whole season, and in the second type of case if the patient can remain there indefinitely. Patients with pollen or mold asthma become completely symptom free in an area in which the given pollens or molds do not exist. Second, the warm dry even climate of Arizona, New Mexico, and southern California, for example, is often highly beneficial to asthmatics with severe sinusobronchitis.

In order to determine whether a given instance of asthma is attributable to environmental or climatic factors, the patient should be hospitalized. If he becomes free of symptoms, climatic factors can be ruled out as the cause of the disease. On the other hand if the attacks are alleviated in an air conditioned room with careful control of temperature and humidity, change of climate may be earnestly considered. This does not, of course, apply to pollen and mold cases. As Black²⁴² says with respect to change of climate for the asthmatic, "Unless one knows from what he is running away his move is a desperate gamble, if he does know, he should be able to take care of it at home."

(3) *Physiotherapy*

It is of great importance to teach the patient to discipline himself during the attack especially with regard to breathing and to combating the panic caused by the feeling of suffocation. The patient must learn to exhale and inhale with quiet, rhythmic, and not jerky respiratory movements.

Above all it is essential to strive, during the

intervals between attacks for relaxation of the tense and hypertrophic musculature involved in breathing as well as for development of the abdominal type of respiration to counterbalance the existing costal predominance. All this can be achieved by appropriate breathing exercises. The aim is to change the respiratory rhythm so that the duration of expiration becomes longer than that of inspiration, and to employ the diaphragm for inspiration and the abdominal musculature for expiration. The most important studies on remedial breathing exercises have been contributed by Hofbauer²⁴³ and the following descriptions are largely based on his observations. Livingstone and Gillespie²⁴⁴ have also reported excellent clinical results from methodical breathing exercises.

SYSTEMATIC TRAINING IN BREATHING The patient is instructed to take the deepest possible inspiration through the nose and then to hum—that is to keep his mouth closed and to accompany expiration through the nose with a slight humming sound. Thereafter he is to wait quietly for a few seconds with his mouth closed until he feels capable of again performing the exercise. In the beginning this procedure is repeated three or four times in succession.

These breathing exercises should be performed three times daily and invariably before meals since a full stomach offers too much resistance to the diaphragm. All of this effort should be smooth and rhythmic without any visible motion of the shoulders or of the chest. Furthermore the patient must be trained to use his diaphragm for breathing since asthmatic individuals are generally accustomed to thoracic respiration only. It must be made clear to the patient that the abdomen is to be drawn in during each expiration and that this is to be done slowly and evenly. When the expiration is completed the patient must next relax his abdominal muscles and allow the abdomen to assume its normal position. Inspiration now begins in the course of which the abdomen protrudes. Thereupon the exercise is repeated. Expiration should take two to four times as long as inspiration and must be accompanied by humming. These exercises must not be continued too long however because the patient may become hyperpneic and dizzy. After a few days the patient should be able gradually to increase the number of breaths until a capacity of ten breaths is reached. While these exercises are done in the standing position at first they should later be performed while walking in the course of which the mouth must always remain closed and every effort should be made to avoid visible respiratory motion.

In severe cases the first step in treatment consists of complete vocal rest for a day or two.

²⁴¹ SHULMAN M H. *New England J Med* 226: 260 1942.

²⁴² LIVINGSTONE J L and GILLESPIE M. *Lancet* 2: 55 1935.

At this point the writers wish once again to stress that they are in complete agreement with Hofbauer on the point that all breathing exercises must be performed through the nose and not through the mouth. The inhaled air that passes through the long nasal route is adequately warmed, humidified, and freed from dust, as a result of which the irritating effect of the air on the bronchial mucous membranes is considerably reduced. Furthermore, these methodical breathing exercises serve to "harden" the nasal mucosa so that it will no longer react with swelling and irritation to exposure to cold air, for example. The prevention of this nasal irritation is all the more significant since it is communicated, via the nasopulmonary reflex, to the bronchial mucosa. In other words, the hardening of the nasal mucosa through these exercises is of more than local benefit.

Patients who have mastered the technic of these exercises are not infrequently able to "hum away" an imminent attack, as well as to stop coughing, by means of short humming expirations and slow inspirations through the nose. However, it usually takes a long time until the patient learns to return to physiologic respiration so completely that it becomes second nature with him, and so that he automatically breathes in this manner even during physical exertion.

Other physiotherapeutic methods have been employed. Bisquert et al.²⁴² employ mechanical and manual massage, and educative and corrective respiratory exercises, while Weiser²⁴³ favors massage and rhythmic compression of the thorax, in conjunction with breathing exercises and regulated gymnastics. As a result of these measures, expiration is facilitated, vital capacity increased, emphysema prevented, and musculature and circulation improved. Physiotherapy can be begun even during an attack, but must be continued for months or years if the improvement is to be maintained.

Since the thorax often becomes rigid in chronic asthma, Ylppö²⁴⁴ and other authors recommended intensive therapeutic gymnastic exercises to render the thorax more mobile.

Ylppö devised the two-bottle system to accustom children to deep breathing.

TECHNIC Two bottles, each of a capacity of about 2 liters, are connected with rubber tubing, and one of them is filled with water. The child blows air into the full one through the mouthpiece of a rubber tube. This pressure forces the water to flow through a glass tube into the other bottle. The second container may also be elevated somewhat, in which case the expiration must be even more vigorous.

After a few months of this exercise, the thorax becomes less rigid, the chronic bronchitis improves, and the asthma attacks become milder in the majority of children. Gay²⁴⁵ reported satisfactory results with this method.

Another very helpful device, particularly for the treatment of chronic bronchitis asthma, is the pneumatic chamber. It is a hermetically sealed air-tight chamber made of steel or reinforced concrete in which a positive pressure of 0.4 atmosphere is attained through the introduction of compressed air. This pressure causes the bronchi and the bronchioles to expand, thus relieving the bronchial spasm. According to Barach and Swenson,²⁴⁷ the bronchial lumens become 1 to 2 mm. wider as a result of breathing under these conditions. At the same time the diaphragm is lowered, so that the lungs can expand, thus permitting deeper breathing. However, not only does inspiration become deeper and easier, but expiration is also prolonged. Moreover, the increased blood flow through the bronchial mucosa definitely favors expectoration; furthermore, the circulation is relieved and cardiac action improved.

The idea of aiding a patient who is struggling for air by supplying air is so apparent that it was already attempted centuries ago by ingenious and pioneering spirits. The first pneumatic chamber is said to have been built of brick in the seventeenth century in England, by Henshaw. French investigators then developed the idea of treatment by means of compressed air. But it was not until the end of the last century that technically perfect pneumatic chambers were constructed of steel. Unfortunately, only very few institutions in this country have such facilities.

Finally, it should be mentioned that di-

²⁴² BISQUERT, L., BUSTAMANTE, W., and MEYER, O. *Rev. chilena de pediat* 14: 484, 1943

²⁴³ WEISER, H. I. *Arch. Phys. Therapy* 25: 461, 1944

²⁴⁴ YLPPÖ, A. *Duodecim* 45: 178, 1929

²⁴⁵ GAY, L. N. cited by UNGER, L. *Ann. Allergy* 3: 133, 1945

²⁴⁷ BARACH, A. L., and SWENSON, P. C. *Arch. Int. Med.* 63: 946, 1939

athermy to the chest sometimes enables patients with bronchitis asthma to raise sputum more readily

(4) *Surgical Measures*

Operations on the nose sinuses, and tonsils in asthmatic patients have been discussed in the relevant sections and bronchoscopic treatment has been described on page 633

Here we shall confine discussion to those surgical measures that aim to interrupt the pathways between the central nervous system and the bronchi—in other words, to abolish the bronchoconstrictor impulses. The physiologic basis for the surgical treatment of asthma has been reviewed by Miscal and Roventine.²⁴¹⁸ Needless to say, surgical intervention of this kind is fraught with considerable danger, and should be restricted to patients for whom all possible methods of therapy have been exhausted, who are critically ill, and in constant danger of death from asphyxia as a result of obstruction of the bronchi by tough mucous plugs and from cardiac failure.

The following operative procedures have been employed: unilateral sympathectomy, unilateral vagotomy, unilateral stellate ganglionectomy, and unilateral and bilateral posterior pulmonary 'plexectomy'.

Unilateral sympathectomy, performed by Kuemmel in 1923, and right vagotomy, performed by Kappis in 1924, have subsequently been repeated in many hundreds of cases by numerous authorities (Hesse²⁴¹⁹). After the first wave of enthusiasm died down as a result of the disappointing fact that permanent benefit could not be achieved from these measures, operations of this kind were abandoned. On the other hand unilateral and especially bilateral stellectomy, according to Leriche and Fontaine,²⁴²⁰ often produce highly satisfactory results. Malherbe²⁴²¹ and Tapella²⁴²² obtained good results with procaine and alcohol infiltration respectively, into the stellate ganglia on one or both sides. Gay

and Rienhoff²⁴²³ tried bilateral resection of the posterior pulmonary plexus in 21 patients and reported that 8 of them were strikingly benefited, 4 experienced no relief and 9 died after the operation. These authors state that the entire pulmonary plexus on both sides must be completely resected if real relief is to be expected for the anatomic and physiologic observations point to a dual innervation of each lung, passing through both the vagus and the sympathetic trunks.

Another important question concerns the type of anesthesia to be employed when any kind of surgery is required in the case of asthmatic individuals. Andre and Grove²⁴²⁴ found general anesthesia safe provided the patients were properly selected and prepared, and an operative method used that combined light anesthesia with carbon dioxide and oxygen hyperventilation. Gay and De Takats prefer ether, for the reason that it readily abolishes vagal reflexes while Prickman²⁴²⁵ is of the opinion that it should be avoided in cases in which asthma is secondary to bronchitis because it tends to produce bronchial irritation and thus to pave the way for postoperative pulmonary complications. Prickman and Gelbach²⁴²⁶ advocate spinal or intra-venous anesthetics in the infectious types of asthma. Preoperative control of cough with out opiates, elimination of offending allergens, both inhalant and nutritional, and avoidance of exertion, temperature changes, dust, and smoke tend to reduce postoperative complications. It is frequently advisable to postpone operation on such patients until warm weather. In a series of 142 asthmatics subjected to major surgical procedures six cases each of postoperative pneumonia and atelectasis developed and severe asthma in four.

When local anesthesia is necessary, the physician should first ascertain by means of intracutaneous tests that there is no hypersensitivity to the drug he plans to use. Allergies of this kind are not at all rarely

²⁴¹⁸ MISCAL L. and ROVENTINE E. A. *Surgery* 13: 495 1943

²⁴¹⁹ HESSE E. *Immunität Allergie u. Infektionskr.* 4 (suppl.) 116 1933

²⁴²⁰ LERICHE R. and FONTAINE R. *Pressemed* 47: 241 1939

²⁴²¹ MALHERBE A. *ibid* 47: 1398 1939

²⁴²² TAPPELLA P. A. *Prensa méd argent* 27: 1553 1940

²⁴²³ GAY L. N. and RIENHOFF W. F. *Bull Johns Hopk ns Hosp* 70: 386 1912

²⁴²⁴ ANDRE R. and GROVE R. C. *J Allergy* 5: 336 1934

²⁴²⁵ PRICKMAN L. E. discussion to Gaarde, Prickman and Rast *Rowek* *

²⁴²⁶ PRICKMAN L. E. and GELBACH P. D. *U. C. l. o. North Amer ca* 28: 991 1944

encountered, especially in relation to procaine and other cocaine derivatives, while occasional instances of hypersensitiveness to epinephrine have also been observed.

In connection with these remarks, it should be added that the risk of operating on asthmatic patients for the various surgical indications is not too great, provided they have received adequate preoperative care (Gaarde et al.¹²⁷). However, asthmatics who undergo upper abdominal operations are more likely to suffer postoperative pulmonary complications, including severe exacerbations of the attacks, than are those who have lower abdominal operations. Needless to say, surgery should, if possible, always be performed during a symptom-free interval, or the attack should at least be properly controlled before surgery is attempted.

18. PROGNOSIS AND RESULTS OF TREATMENT

The questions as to the prognosis in asthma and the efficacy of therapy are by no means easy to answer.

If one were to remain content with the patient's status at the time of discharge, either from the hospital or from ambulatory treatment, one could say that the majority showed considerable improvement or even entire freedom from symptoms. Unfortunately, however, this means nothing at all, since more or less severe relapses almost always occur sooner or later. It is more informative, therefore, to discuss the clinical results in the various forms of asthma.

The large group of allergic asthma, including that due to pollen, is today readily amenable to treatment. Suitable prophylactic hyposensitization and deallergization methods are capable of producing really satisfactory results. The prognosis is good here, and absolute "cure" is possible. The same is true when the allergens are such that they are easily avoidable.

Bronchitis asthma will also, to a great extent, respond to treatment. But certain special factors must be considered here. For one thing, therapy should be instituted as early as possible, otherwise chronic bronchitis and emphysema may have reached such a

point that complete recovery is difficult, not to say impossible. Furthermore, the predisposing factors and contributory causes must always receive due consideration, and both metaspecific and nonspecific measures should be given the attention that their importance merits.

Psychogenic asthma is curable only if the physician can succeed in removing or alleviating the underlying psychic factors, a feat that is not always possible. Nevertheless, an understanding physician can often achieve great and lasting relief in such patients.

The greatest difficulty, however, is presented by the pathergic forms in which a marked nonspecific hyperirritability of the bronchial mucosa has usually developed. Here iodides, cardiotherapy, peptone and tuberculin hyposensitization, fever treatments, respiratory exercises, pneumatic chambers, and the like, play the most important part. The prognosis is, as a rule, not too favorable for this group, for every cold, or any exertion or excitement, is capable of evoking new attacks. On the other side of the ledger is the fact that even very severe attacks are rarely dangerous to life. It is true that several hundred deaths have been reported in the past few years, but these represent only a very small mortality rate in view of the millions of patients suffering from asthma. Most dangerous, in this respect, is the use of morphine, to which many succumb every year.

A particularly weighty factor is whether or not emphysema, bronchiectasis, or myocardial damage is present. These conditions definitely do abbreviate the span of life.

Also of great significance in relation to the prognosis are the patient's personal character and, regrettably, his financial situation. It is certainly easier to achieve marked improvement if the patient is energetic and intelligent, and at the same time cooperative—and, above all, if he is in a position to take proper care of himself.

All in all, it may be said that asthmatics reach a relatively advanced age, provided, of course, that the physician is able to keep the condition under control. However, life insurance analyses by Old,¹²⁸ and by Dublin

¹²⁷ GAARDE, F. W., PRICKMAN, L. E., and RASZKOWSKI, H. J.: J.A.M.A. 120: 431, 1942.

¹²⁸ OLD, H.: J. Allergy 4: 172, 1933.

and Marks,²⁴⁹ reveal a higher ratio of actual deaths than would be expected statistically. They blame it on the resultant cardiac disease.

Lastly, certain other data may be of interest here. Rackemann²⁴³⁰ reported 213 cures at the end of two years among 1,074 cases, representing approximately 20 per cent, by the end of four years, the proportion of the original number still free from symptoms was only 12 per cent. Unger²⁴³¹ reported the following final results in a series of 207 cases: 20 per cent were symptom-free after one year or longer, 50 per cent showed improvement, and 10 per cent had died—but only 6 out of these 20 individuals had died of asthma. Recently Unger and Wolf²⁴³² reported on an additional 252 cases with approximately the same findings. It is significant that the outlook for life and for freedom from symptoms was far worse in the cases that had been classified as "chronic" in comparison with the 'paroxysmal' group. Witts²⁴³³ also arrived at a value of 20 per cent of cures. However, Vaughan¹ warns "Of any group, 85 or 90 per cent may still be having difficulty six years later."

From this it may be seen that it is extraordinarily difficult to decide whether an asthma patient has been cured or merely freed of his symptoms.

In conclusion, one more important point must be considered. The great majority of physicians are of the opinion that asthma is not a dangerous but practically an incurable disease. Although they naturally refrain from expressing this opinion to the patient, the latter very soon senses this pessimistic attitude, which often does immeasurable harm psychically and consequently physically. The physician who is convinced that many cases can be cured and that almost all can be considerably improved, and who is able to communicate this conviction to his patient, possesses the most important prerequisites for success.

B ALLERGIC BRONCHITIS

Much that has been said with respect to asthma, particularly concerning the pre-

disposing and precipitating factors, also applies to allergic bronchitis. The first organized discussion of this condition was contributed by Waldbott²⁴³⁴ along with a report of 10 cases. Van Ordstrand and Ernstene²⁴³⁵ and Thomas and Taylor²⁴³⁶ have analyzed series of 60 and 100 cases, respectively. In addition, numerous other reports have appeared.

Although not nearly as common as asthma, allergic bronchitis is by no means rare. It can arise at any age, but appears to be somewhat less frequent in the first two decades of life as compared to asthma. There are no significant differences in the sex incidence.

The pathology of this condition is unknown. Presumably, the allergic reaction results in a localized edema and dilatation of the blood vessels of the bronchial mucous membrane along with bronchorrhea. Apparently there is no bronchospasm.

With regard to predisposing factors, a positive family history of allergic diseases is obtained in a considerable proportion of patients, indicating a constitutional predisposition. Moreover, a very high percentage of the cases have or have had one or more other allergic diseases, most notably allergic rhinopathy, but also frequently including hay fever, asthma, urticaria, angioneurotic edema, neurodermatitis, infantile dermatitis, and migraine. In addition, preceding upper respiratory infections, such as coryza, influenza, pertussis, and pneumonia, or operations on the nose, paranasal sinuses, or tonsils often appear to pave the way for bronchial sensitization.

The etiologic agents are predominantly the inhalant allergens, chiefly house dust, feathers, cottonseed, animal danders, and orris root. When the causative substance is seasonal, such as pollens or molds, the condition is naturally seasonal in its occurrence. Some instances of "winter bronchitis" may also be examples of allergic bronchitis, as in a case of Vaughan's²⁴³⁷ who was sensitive to house dust and feathers, but with seasonal symptoms. Other cases have perennial manifestations with seasonal fluctuations. Foods are of much less importance, while the possibility of bacterial hypersensitiveness as a cause requires

²⁴²⁹ DUBLIN, L. I. and MARKS, H. H. Mortality of Risks With Asthma. *A Life Insur. Med. Directors Am.* 1934.

²⁴³⁰ RACKEMANN, F. M. *Arch. Int. Med.* 50: 819, 1932.

²⁴³¹ UNGER, L. *J. Allergy* 7: 364, 1936.

²⁴³² Idem and WOLF, A. A. *J. A. M. A.* 121: 325, 1943.

²⁴³³ WITTS, L. J. *Lancet* 1: 273, 1936.

²⁴³⁴ WALDBOTT, G. L. *J. Lab. & Clin. Med.* 13: 943, 1928.

²⁴³⁵ VAN ORDSTRAND, H. S. and ERNSTENE, A. C. *M. Clin. North America* 22: 319, 1935.

²⁴³⁶ THOMAS, J. W. and TAYLOR, R. V. *Ann. Allergy* 1: 185, 1943.

further investigation. The intelligent and observant patient will not rarely be cognizant of the responsible agent. Thus, the junior author has seen a 32 year old man with recurring paroxysms of cough and mucoid expectoration of four years' duration which were stated by the patient to be due to drinking coffee. Personal and family histories for other allergies were entirely negative. Intradermal skin test with coffee extract and Prausnitz-Kuestner passive transfer were markedly positive. Avoidance of the beverage led to complete disappearance of symptoms within 48 hours, and on three subsequent occasions indulgence was followed by paroxysms of cough. The senior writer observed the case of a 45 year old physician who had a most severe bronchorrhea. The sputum contained an abundance of eosinophilic cells. The colleague was treated for bronchiectasis for a long time without results. Finally an autogenous sputum vaccine brought lasting cure (observation time, five years).

The outstanding symptom of allergic bronchitis, as already indicated, is cough, which may be chronic, recurring, spasmodic, or paroxysmal. In some instances, an explosive quality is present. The expectoration consists of varying amounts of mucoid sputum, and rarely of mucopurulent material. Occasionally the sputum is blood-streaked during an especially severe paroxysm. Not infrequently, however, the cough is entirely nonproductive and of a hacking nature. At times, the cough is so severe that vomiting supervenes. Generally, cough and expectoration are greatest on first arising in the morning and on retiring, and almost always exacerbated during physical exertion. Some minor wheezing, or as some patients more accurately describe it, "rattling" in the chest, may be present at times, but it is neither a consistent nor a prominent part of the symptomatology. Dyspnea, in the absence of complicating asthma, does not occur. Vague discomfort and "soreness" in the chest are a common accompaniment of the cough, and occasionally hoarseness and sore throat appear. Many patients complain of malaise, easy fatigability, loss of appetite, weight loss, and excessive perspiration. Fever is not present except when there is associated infection.

The physical examination is not characteristic. Usually, the lungs are clear and

nothing more will be found than the typical appearance of allergic nasal mucous membranes. Sometimes moderately coarse or coarse gurgling râles are heard, predominantly during inspiration and chiefly at the bases of the lungs. There is no prolongation of the expiratory phase of respiration.

Röntgenograms of the chest often show an increase in the peribronchial and perivascular markings, and a widening of the hilar shadows—but this is not of diagnostic significance. Lipiodol bronchograms may be necessary to rule out bronchiectasis, and sometimes bronchoscopy to differentiate chronic infectious conditions, neoplasms, non-radio-opaque foreign bodies, and the like. Aside from a moderate degree of blood eosinophilia in a small percentage of cases, the routine laboratory studies are not informative. However, we have found the presence of eosinophils in the sputum to be a fairly consistent finding, and decidedly helpful when present.

The differentiation from asthma can be made on the basis of the symptomatology and the physical signs, particularly the absence of significant degrees of wheezing and dyspnea, and of evidences of interference with expiration. Differentiation from other forms of bronchitis is more difficult and may depend largely on the nature of the sputum, the absence of associated signs of infection (preceding coryza, fever, leucocytosis, accelerated erythrocyte sedimentation rate, Weltmann reaction), the presence of sputum eosinophilia, and in border-line cases, on the response to sulfonamide and penicillin therapy. The features of bronchitis asthma and of the sino-bronchial syndrome, and the frequency with which infectious bronchitis complicates bronchial asthma have been accorded sufficient discussion elsewhere. It should also be noted that a mild cough is often present in severe hay fever, presumably due to the postnasal drip. Needless to say, other causes of chronic or recurring cough, including pulmonary, cardiovascular, and mediastinal lesions, should be considered in the differential diagnosis.

In summary, the diagnosis depends on a history of chronic or spasmodic bronchitis, otherwise inexplicable, a previous personal and often family history of other allergic diseases, frequently a finding of eosinophils in the sputum and sometimes of blood eosino-

philia, and the exclusion of other diagnostic possibilities by appropriate methods

As noted elsewhere (p 563), this condition is intimately related to allergic mucosal involvement of the upper respiratory tract giving rise to allergic cough—in fact, the only basic difference is one of the location of the sensitized tissue. There is no doubt that many of the cases are really instances of allergic tracheo-bronchitis.

The relationship of allergic bronchitis to asthma is a moot question. Colmes and Rackemann²⁰⁹² and Kahn²¹²⁷ consider it to be a preasthmatic manifestation. Certainly, their cases and many others followed for a sufficient length of time ultimately developed unmistakable asthma, particularly if untreated. On the other hand, many patients observed for years, persist with uncomplicated allergic bronchitis without even remote evidence of asthma. There is considerable reason to think that allergic bronchitis predisposes to, or actually is the fundamental cause of bronchiectasis (Watson and Kibler²¹¹⁸ and others). Emphysema is not a common complication.

The methods of establishing the etiologic diagnosis conform with those used in asthma (p 627). We shall merely warn against undue dependence on skin tests, and recommend, in addition to a carefully taken history, the employment of bronchial environmental, avoidance and re exposure tests.

Treatment should follow the recognized methods, depending on the causative factors, with particular emphasis on avoidance and elimination when feasible. The usual expectorant drugs are often singularly ineffective. Hyposensitization generally gives satisfactory results. Thomas and Taylor²¹³⁶ found that the response to therapy was better when the symptoms had existed for less than three years, in individuals under 30 years of age, and possibly when there was marked blood eosinophilia. The prognosis is favorable in the majority of properly treated cases.

C ALLERGIC DISEASES OF THE LUNG

1 ALLERGIC PNEUMONIA

As early as 1912, Schlecht and Schwenker²¹²⁸ observed that extensive eosinophilic pneu-

monias appeared following intratracheal administration of the antigen in intraperitoneally sensitized animals. Friedberger and Busson reported the production of "sterile anaphylactic pneumonia" in guinea pigs allergized to horse serum, following insufflation of horse serum into the trachea. More recent experiments have shown that the manifestations of allergic pneumonia in animals assume a variety of forms. Some of the animals present ordinary lobar pneumonia (Fried²¹²⁹), often associated with fibrinous-exudative pleuritis (Nomura), while others develop focal pneumonia (Krauspe and Thies) or interstitial pneumonia (Ishiooka). In highly sensitized animals, the most important pathologic findings in allergic pneumonia are extensive hemorrhages aggregations of large numbers of eosinophilic cells, perivascular accumulation of histiocytes, "fibrinoid swelling" of the intima of the vessel walls, emphysema, and atelectasis (Walther²¹⁴⁰). According to Cannon et al,²¹⁴¹ the primary effect of the antigen-antibody reaction in the lungs is an increased capillary permeability.

Moreover, allergic manifestations in the lungs can also be elicited when the reinjection is given into the pleural cavity (Michelazzi). Lastly, these responses can also be evoked by way of the blood stream. Thus, in perfusion experiments on the isolated lungs of dogs that had been treated three weeks previously with polypeptides, Burstein and Olivier²¹⁴² produced atelectasis and infarcts by employing citrated blood to which a solution of the same polypeptides was added. Animals that had not been sensitized showed few, if any, changes in the lungs following the same procedure.

With regard to human beings relatively few observations suggesting the existence of pneumonia of allergic origin have as yet been made. Pilz²¹⁴³ for one, observed pulmonary lesions with fever that both clinically and roentgenologically simulated pneumonia, following administration of nirvanol, he interpreted these as manifestations of an allergic exanthem of the bronchial mucosa. Ellis and Mc

²¹²⁹ FRIED B M Arch Path 18 865 1934

²¹⁴⁰ WALTHER G Ztschr f d ges exper Med 106 748 1939

²¹⁴¹ CANNON P R WALSH T E and MARSHALL C E Am J Path 17 777 1941

²¹⁴² BURSTEIN M, and OLIVIER C Compt rend Soc de biol 125 961 1937

²¹⁴³ PILZ K Arch f Kinderh 82 210 1927

²¹²⁷ KAHN I S J Lab & Clin Med 12 1197, 1927

²¹²⁸ SCHLECHT H and SCHWENKER G Arch f exper Path u Pharmacol 68 163 1912

Kinlay²⁴⁴ and Gravesen²⁴⁵ each reported a case of massive migrating atypical pneumonia of unusual duration, presenting a marked eosinophilia and accompanied by high fever that was grossly disproportional to the degree of prostration. Hypersensitiveness to prontosil was discovered to be the cause in both instances. Cole and Korns²⁴⁶ observed an instance of bronchopneumonia in a child, with recurring angioneurotic edema and an eosinophilia of 54 to 84 per cent, they hazarded the opinion that this picture might be an expression of angioneurotic edema of the lung. Vaughan and Hawke²⁴⁷ also reported a case with roentgen changes in the lung, which, in view of the rapid disappearance of the symptoms, was interpreted by these authors as attributable to angioneurotic edema. Castle-den and Hamilton-Paterson²⁷³ described under the term "bagassosis" a series of cases of an acute, afebrile pneumonic disease caused by a protein antigen in the dust of bagasse—the broken stalks of sugar-cane employed as an insulating material. Skin tests were positive. Resolution of the pulmonary lesions was sometimes long delayed.

According to Waldbott and Snell,²⁴⁴ pulmonary infiltrations resembling bronchopneumonia may arise as the result of allergic shock and of severe asthma, especially in young children. In attempting to differentiate this type of pneumonia from other pulmonary lesions, the following clinical features were found to be of diagnostic significance: the presence of an afebrile stage, with collapse and associated asthmatic symptoms; less severe systemic manifestations and a shorter duration than in ordinary pneumonia; and a relatively low leucocyte count at the beginning of the febrile period. This concept is of definite importance, from both diagnostic and therapeutic viewpoints. First, it indicates that a history of "pneumonia" in an allergic child, particularly at the time of the first attack of asthma, may refer to an allergic pulmonary reaction rather than to a primary infection. Second, in treating such "pneumonia," repeated small doses of epinephrine to combat

the edema, and elimination of contact with the allergen, may be of paramount value and may even constitute a life saving procedure.

Lastly, mention is still to be made here of the reasons that lead Lauche,²⁴⁸ Renaud,²⁴⁹ and other investigators to regard lobar pneumonia as the result of sensitization to pneumococci. The various forms that this disease takes suggests the idea that they may be attributable to different states of reactivity of the body. The newborn infant is not capable of reacting to a pneumococcal infection with exudation, as is the case later in life, the infection therefore expresses itself in the form of a sepsis. In young nursing infants, pneumococcal infection of the lung presents the picture of a disseminated focal pneumonia; in nursing infants in the first year of life, more or less confluent foci are formed, while it is only in older children that the typical picture of lobar pneumonia is observed. Furthermore, in adults as well as in children, the same micro-organism can elicit in one case characteristic lobar pneumonia, with the usual febrile course and alveolar exudates, in another, small foci of inflammation, with atypical fever and varyingly constituted exudates, and in still others, only central involvement. The pneumonic lesion, therefore, varies according to the body's immunologic state.

Lauche, as well as Renaud, assumes that repeated minor infections with pneumococci, in the course of common colds or grippe, sensitize the organism, and that when there is reinfection of the respiratory tract with pneumococci, pneumonia results. Fibrinous pneumonia is thus to be regarded as the reaction of a sensitized individual to the pneumococcus or its products. There are two distinct phases in this disease: the first, present in the beginning, is the specific phase, expressed by edema of the alveoli, followed by marked engorgement (stage of red hepatization), the second is that of gray hepatization, characterized by leucocyte invasion of the exudate present in the alveoli. The first phase represents the allergic reaction; the second and successive phases are the same as those encountered in all other inflammations of the lung. Experimentally it is never possible to produce pneumonia with the very first injection of pneumococci.

²⁴⁴ ELLIS, R. V., and MCKINLEY, C. A.: *J. Lab. & Clin. Med.* 26: 1427, 1941.

²⁴⁵ GRAVENSEN, P. B.: *Acta med. Scandinav.* 96: 523, 1938.

²⁴⁶ COLE, J., and KORN, H. M.: *J. Allergy* 5: 347, 1934.

²⁴⁷ VAUGHAN, W. T., and HAWKE, E. K.: *ibid.* 2: 125, 1933.

²⁴⁸ WALDBOTT, G. L., and SNELL, A. D.: *J. Pediatr.* 6: 229, 1935.

²⁴⁹ LACHE, A.: *Lungenentzündungen*. In *Handb. d. path. Anat.*, 1928.

²⁵⁰ RENAUD, M.: *Deutsche med. Wochschr.* 63: 167, 1937.

This brings on only a local inflammation which is followed under certain conditions by septicemia. On the other hand repeated injections of pneumococci in partially immunized animals can produce diseases of the lungs corresponding to pneumonia in human beings (Sharp and Lake De Wadsworth Stillman and Bransch).

Rich and Gregory³¹ found that experimentally produced rheumatic pneumonitis was basically identical with the pneumonitis caused by sulfonamide sensitivity and that both exhibit the primary capillary damage characteristic of focal anaphylactic reactions. They consider this evidence in support of the view that rheumatic pneumonitis may be allergic in origin.

2 TRANSIENT PULMONARY INFILTRATIONS

(LOEFFLER'S SYNDROME)

Loeffler^{32a} first called attention to a clinical syndrome characterized by transient and migrating pulmonary consolidations by the comparative absence of symptoms and physical signs and by the presence of a blood eosinophilia ranging from 10 to 60 per cent. There is rarely any fever and the general condition is virtually undisturbed. The consolidations persist for only a few hours or at the most for three to eight days and may be followed by similar involvement of other portions of the lungs. The sputum often contains large numbers of eosinophils. To this description Hansen Pruss and Goodman^{32b} after an analysis of six cases added the following features: leucocytosis as well as eosinophilia, persistent severe asthma, lack of responsiveness to the known sulfonamide compounds and a history of frequent upper respiratory infections. However Breton^{32c} and others found that asthma is not an essential feature of the syndrome.

This condition has been referred to by a variety of terms including transitory pulmonary infiltrations associated with eosinophilia, allergic pneumonia, eosinophilic infiltration of the lungs, allergic pulmonary consolida-

tions, eosinophilic lung and edema allergicum pulmonis, thereby leading to some confusion.

The diagnosis of these cases always requires the use of roentgenograms of the chest. The fleeting migratory shadows may be extensive and irregular in shape or small and round; they may be fleecy or dense, unilateral or bilateral and may involve the entire lung or be limited to one lobe. Hennell and Sussman^{32d} found the roentgen features to consist of areas of homogeneous density of varying size simulating tuberculous suppurative bronchopneumonia or phases in the course of Boeck's sarcoid. Narrow platelike densities are frequently seen extending obliquely caudad and laterally, a type of shadow that seems to be unique to this condition. They believe that certain cases occur in connection with peritubercular nodosa and may terminate fatally.

It was once believed that these consolidations were caused by bronchial spasm combined with secretory stagnation. This coincided perfectly with the concept of local atelectasis due to bronchial occlusion as a transitory process, dense enough to cast a shadow in the roentgenogram. The earlier assumption that edema or atelectasis is the underlying anatomic change has been superseded by von Meyenburg's^{32e} postmortem studies on four accidental deaths. He found that infiltrations were of pneumonic type with exudation into the alveoli and with eosinophilic infiltration of both the alveoli and the interstitial tissue, justifying the existing clinical impression that the lesion is a consolidation. There was also an inflammatory involvement of the pleura and interlobar fissures. Tubercle bacilli and Ascaris larvae were not demonstrable. In Waldbott's^{32f} case the sections from the lungs showed small areas of edema infiltrated with leucocytes at their periphery. Gravesen^{32g} states that it is the interstitial tissue of the lung that is hypersensitive.

While Loeffler was inclined to believe that various etiologic agents were operative, Engel^{32h} on the basis of a very interesting observation assumed the condition to be attributable to an underlying allergy. In Shanghai Engel observed that each year at the

³¹ RICH A. R. and GREGORY J. E. *Bull. Johns Hopkins Hosp.* 73: 46, 1943.

^{32a} LOEFFLER W. *Ber. z. klin. u. Tuberk.* 79: 368, 1937.

^{32b} HANSEN PRUSS O. C. and GOODMAN E. G. *Ann. Allergy* 2: 82, 1944.

^{32c} BRETON A. *Par. méd.* 28: 538, 1938.

^{32d} HENNEL H. and SUSSMAN N. *Radiology* 44: 328, 1945.

^{32e} MEYENBURG H. *ow. Schweiz. med. Wchnschr.* 72: 809, 1942. *abstr. JAMA* 121: 6, 6, 1943.

^{32h} ENGEL D. *Ber. z. klin. u. Tuberk.* 87: 239, 1936.

end of May an appreciable percentage of the population was afflicted with a characteristic cough. This condition was known as "privet cough" among laymen, for they assumed that it was caused by the pollen of the bush *Ligustrum*. The disease begins with headache, moderate fever, and a cough with a clear yellow sputum. The physical findings are slight, the general condition is good. Roentgenologic examination reveals intense shadows, sometimes isolated, sometimes multiple, usually small, but occasionally extending over an entire lobe—in short, a picture similar to that of pneumonia or of an early tuberculous infiltration. The pulmonary changes often disappear within twenty-four hours, sometimes in a few days. The strict dependence on the season, and the high degree of eosinophilia, strongly suggest an allergic origin. The real cause is unknown; skin tests with privet pollen are negative. Meyer²⁴³ also considered the etiology to be pollen sensitivity.

Since the publication of these reports, numerous similar cases have been described, particularly in children (Soederling,²⁴⁹ Weber,²⁴⁶ Smith and Alexander²⁴¹), though also in adults (Stefano,²⁴² Hoff and Hicks,²⁴³ Lavier et al.,²⁴⁴ Baumann,²⁴⁵ Jones and Souders,²⁴⁶ Miller²⁴⁷). In some of these patients, parasites (ascaris, amebae, *Fasciola hepatica*) were found in the intestines. Since intramuscular injections of emetine in a case of typical Loeffler's syndrome produced a dramatic clearing, Randall²⁴⁸ raised the question whether, in districts where amebiasis is endemic, the condition may not be of amebic origin. Wright and Gold,²⁴⁹ on following 15 cases of creeping eruption (cutaneous helminthiasis due to *Ancylostoma braziliense* or larva migrans) by means of serial X rays of the chest, found Loeffler's syndrome in 9.

Similar findings have also been reported in association with trichinosis (Slowey²⁴⁷⁰), chronic brucellosis (Elsom and Ingelfinger²⁴⁷¹), bronchitis and asthma (Smith²⁴⁷²), and tuberculosis (Leitner²⁴⁷³).

The pulmonary manifestations were considered by these authors to be an expression of allergy, and in some cases of infestation allergy. It has long been known, of course, that direct pulmonary involvement occurs in the course of infestation with *Strongyloides stercoralis* and with *Necator americanus* (Berl²⁴⁷⁴). Hence, careful and thorough study of the sputum and stools for ova and parasites is advised in every case in which transitory pulmonary infiltrations appear associated with eosinophilia. However, considerable evidence rules out this possibility in true Loeffler's syndrome and favors the concept of an allergic etiology. Wright and Gold²⁴⁹ found no ova or parasites in the stools in their cases despite repeated examination over a period of time, and most of their patients reacted to skin tests with extracts of nematodal parasites. Zweifel²⁴⁷⁵ demonstrated sensitivity to Ascaris extract in a significantly larger percentage of cases of Loeffler's syndrome than in normal persons or those with ascariasis. In Maier's²⁴⁷⁶ series of 100 cases, over half displayed other allergic manifestations either before or at the time of the illness. Incidentally, he found only 2 patients with active tuberculosis.

It is apparent from the above discussion that transitory pulmonary infiltration with eosinophilia is not a disease in itself, but rather an expression of an allergic reaction in the body. Since no uniform cause has been demonstrated, the diversified list of etiologic factors lends credence to the view that it is an allergic phenomenon.

It should be pointed out that the course is not always acute. The form described by Loehr and by Léon-Kindberg differs in that the symptoms are severe, almost like those of a septic process, and that the course is extremely

²⁴³ MEYER, H. F. *Med. Welt* 11: 1808, 1937.

²⁴⁹ SOEDERLING, B. *Arch. Dis. Childhood* 14: 22, 1939.

²⁴⁶ WEBER, F. P. *Brit. J. Child. Dis.* 36: 15, 1939.

²⁴¹ SMITH, D. C. W., and ALEXANDER, A. J. *South. M. J.* 32: 767, 1939.

²⁴² STEFANO, J. *Semana méd.* 2: 749, 1939.

²⁴³ HOFF, A., and HICKS, H. M. *Am. Rev. Tuberc.* 45: 191, 1942.

²⁴⁴ LAVIER, G., BARIET, M., and CAROLI, J. *Paris méd.* 1: 434, 1939.

²⁴⁵ BAUMANN, H. *Schweiz. med. Wchnschr.* 74: 326, 1944.

²⁴⁶ JONES, S. H., and SOUDERS, C. R. *New England J. Med.* 231: 356, 1944.

²⁴⁷ MILLER, H. *New England J. Med.* 232: 7, 1945.

²⁴⁸ RANDALL, T. *Brit. J. Tuberc.* 39: 37, 1945.

²⁴⁹ WRIGHT, D. O., and GOLD, E. M. *J. A.M.A.* 128: 1082, 1945.

²⁴⁷⁰ SLOWEY, J. F. *Ann. Int. Med.* 21: 130, 1944.

²⁴⁷¹ ELSOM, K. A., and INGELFINGER, F. J. *Ann. Int. Med.* 16: 995, 1942.

²⁴⁷² SMITH, J. H. *South. M. J.* 36: 269, 1943.

²⁴⁷³ LEITNER, S. J. *Acta med. Scandinav.* 97: 473, 1938.

²⁴⁷⁴ BERL, J. E. *Correspondence, J. A.M.A.* 127: 354, 1945.

²⁴⁷⁵ ZWEIFEL, E. *Helvet. med. Acta* 11: 117, 1944.

²⁴⁷⁶ MAIER, C. *Ibid.* 10: 95, 1943.

protracted, persisting for months. Kartagener²⁴⁷⁷ described a case characterized by chronicity and mildness of the symptoms, including indefinite back and chest pains, subfebrile temperatures, nocturnal sweats, and headaches.

The relationship of Loeffler's syndrome to tropical eosinophilia has not been entirely clarified. The latter is a newly recognized disease, endemic in certain tropical regions, and characterized by chronic paroxysmal cough, frequent attacks of asthmatic breathing, weakness, anorexia, weight loss, marked leucocytosis and eosinophilia. The symptoms, physical signs, and response to epinephrine resemble those of asthma. X-ray examination of the chest reveals findings resembling those

of acute miliary tuberculosis, or small bronchopneumonic foci. The etiology is unknown, but the dramatic response to arsenotherapy (neoarsphenamine, mapharsen, carbarsone) suggests a spirochetal or protozoan causation, while the cheese mite, *Tyroglyphus*, has been found in the sputums of some cases. Apley and Grant²⁴⁷⁸ state that any differentiation between this condition and Loeffler's syndrome is more apparent than real, and that the gradation between cases illustrating the two diseases renders it more profitable to consider them as the manifestation of one type of disease process.

In view of this fact, a short course of arsenical therapy may be justified in cases of Loeffler's syndrome. Miller²⁴⁶⁷ reported good results with mapharsen in one case.

²⁴⁷⁷ KARTAGENER, M. Schweiz med Wchnschr 72 862, 1942.

²⁴⁷⁸ APLEY J. and GRANT G. H. Lancet 1 807 1942.

ALLERGIC DISEASES OF THE GASTRO-INTESTINAL TRACT

THE rôle of the gastro-intestinal tract in the pathogenesis of allergic diseases is manifested in three ways. First, under certain physiologic and pathologic conditions, inadequately digested and even unaltered proteins, as well as drugs, may be absorbed by the gastro-intestinal mucous membranes and thus reach the blood stream (Walzer²⁴⁷⁹). While in most individuals this is not followed by untoward reactions, in some the resorbed substances assume antigenic properties. Cases of this kind properly belong in the categories of nutritional or drug allergies, the gastro-intestinal tract is here merely the portal of entry of the allergen. The localization of the clinical response may vary from case to case, depending on which structure is the shock tissue. For example, ingestion of egg may cause an attack of asthma in one instance, migraine in another, and urticaria in a third. Second, the allergic reaction may take place in the gastro-intestinal tract itself, provided the latter is the shock structure. The causative allergens in these cases are, as a rule, foods; sometimes, however, they may be drugs administered either enterally or parenterally, pollens, hormones, biologic preparations, or, lastly, endogenous allergens formed in the digestive tract. Third, gastro-intestinal allergic manifestations may be merely one of the symptoms of an anaphylactic shock or constitutional allergic reaction. As a single example of this type may be cited Derbes and Bruno's²⁴⁸⁰ cases of serum disease simulating acute surgical abdominal conditions.

The clinical manifestations of allergic involvement of the gastro-intestinal tract are determined by the site at which contact with the allergen is most intensive. Any portion of the tract, from mouth to anus, may be affected, and there is reason to believe that not only the mucosa, but also the deeper layers and the vascular structures may be involved. The most commonly observed syndromes are cheilitis, stomatitis, gastritis, enteritis, colitis, and proctitis.

Just a word as to nomenclature at this juncture. The writers do not favor the use of

the terms mentioned, for the reason that the suffix "-itis" is generally understood to designate an inflammatory condition, which the allergic tissue reaction does not present. The terms allergic gastropathy and allergic enteropathy would seem far more appropriate.

For purposes of discussion, it may be convenient to group the different manifestations according to the portion of the tract chiefly involved, despite the fact that it is relatively rare for only the stomach or one part of the intestine to be affected. As a rule, the entire gastro-intestinal tract is more or less involved. On the other hand, it is also true that in many cases the manifestations in one organ are so predominant that both the patient and the physician may be inclined to overlook the other symptoms.

Malnutrition of varying degree occurs in the course of many allergic diseases, but especially asthma, and may be severe enough to dominate the clinical picture, or even, according to Ballestero,²⁴⁸¹ be the sole manifestation of a hypersensitive state. In his experience, about one-third of allergic children under 15 years of age were 15 per cent or more underweight, and some as much as 50 per cent. Loss of weight following the onset of asthma, hay fever, or serum disease is commonly observed. Allergic malnutrition is apparently dependent on anorexia, capricious appetite and food aversions, hypochlorhydria, and disturbances of intestinal motility. Gastro-intestinal sensitivity due to food allergy appears to be a prominent factor in the mechanism. In asthmatics, the absence of adipose tissue is more noticeable in the thorax than in the abdomen. In children under 10 years of age, meteorism is frequently found. Definite improvement in the nutritional state of allergic patients is noted after antiallergic therapy.

It must be stressed here that not by any means is every gastro-intestinal disturbance based on intolerance to some food or drug necessarily to be regarded as allergic. Such a diagnosis is to be made only when ingestion of a certain food or foods, or of a certain drug or drugs, is regularly followed by certain disease

²⁴⁷⁹ WALZER, M. *J. Allergy* 13: 554, 1942.

²⁴⁸⁰ DERBES, V. J., and BRUNO, F. E. *Surgery* 13: 450, 1943.

²⁴⁸¹ BALLESTERO, L. H.; *Semana méd.* 25: 3, 1944.

symptoms when these fail to appear after elimination of the given substance or substances or after appropriate anti-allergic measures and when the symptoms reappear following re-exposure to the suspected agent or agents. Moreover the diagnosis should be confirmed wherever possible by other allergic manifestations such as those appearing on the skin or visible mucosa.

Finally it is of interest to list in Table 56 those symptoms referable to the gastro-intestinal tract that may have an allergic basis.

TABLE 56—Gastrointestinal Symptoms That May Have an Allergic Basis

Site	Syndrome
Lips	cheilitis herpes labialis angioneurotic edema
Mouth	canker sores aphthae stomatitis coated tongue geographic tongue angioneurotic edema of tongue glossitis
Esophagus	cardiospasm angioneurotic edema
Stomach	dyspepsia belching pyrosis epigastric distress burning pain or tenderness nausea vomiting cyclic vomiting pylorospasm pain of gastric ulcer type
Intestines	diarrhea constipation abdominal cramps spastic colon mucous colitis flatulence proctitis pruritus and pain of duodenal ulcer type acute abdominal crises simulating appendicitis

A SYMPTOMATOLOGY

I MOUTH (STOMATOPATHY) AND ESOPHAGUS (ESOPHAGOPATHY)

The mucosa of the mouth (i.e. of the lips, cheeks, gums and tongue) may become sensitized by direct contact with an allergenic agent. The ensuing condition is aptly called contact stomatitis. Far less frequently allergic manifestations of the oral mucosa are caused by foods or drugs reaching the region by the hematogenous route. This latter group includes the canker sores that are not uncommonly observed in association with nutritive allergy in addition to presenting a coated tongue these patients complain of a 'rough and burning sensation in the

mucous membranes of the mouth a condition that is almost entirely subjective (Duke⁵⁰⁰ Rowe⁵⁴⁸). Lastly allergic diseases of the buccal mucosa may appear simultaneously with cutaneous manifestations. Particularly in hypersensitivities to hypnotics responses range all the way from trivial enanthems on the buccal mucosa to vesicular and ulcerative stomatitis (Chargin²⁴⁵³ Wise²⁴⁵⁴ Urbach and others). Watson Williams²⁴⁸⁵ reported purpura and faucial lesions attributable to hypersensitiveness to neoarsphenamine.

Needless to say the contact type is by far the more commonly encountered. There is an

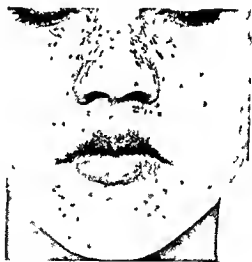


FIG. 299 CHEILITIS DUE TO LOCAL HYPERSENSITIVENESS TO LIPSTICK

extensive literature (Sulzberger et al.²⁴⁹⁶) regarding allergic cheilitis a condition that is almost invariably based on an underlying epithelial allergy. Most of these cases are due to lipstick and most commonly the dye is in turn the allergenic component (Fig. 299). The perfume has been found to be the responsible ingredient in relatively few cases (H. Baer). Particularly interesting is a case reported by M. F. Engman Jr. in which the lipstick reached the patient's lips by way of a kiss.⁵⁴⁸⁵ The condition has also been caused by

⁵⁰⁰ ROWE A. *Am J Med Sci* 183: 529 1932

⁵⁴⁸ CHARGIN L. *Arch Dermat & Syph* 6: 222 1922

²⁴⁵⁴ WISE F. *ibid* 13: 431 1926

²⁴⁸⁵ WATSON WILLIAMS E. *J Laryng & Otol* 53: 181 1938

²⁴⁹⁶ SULZBERGER M. B. and GOODMAN J. *Arch Dermat & Syph* 37: 597 1938

tooth paste, mouth wash, lozenges, and secretures (Templeton,²⁴⁵⁷ L. S. Beinhauer), preparations containing oil of cinnamon or oil of cloves (E. D. Osborne), applied to the gums in pyorrhea, dental plates (Cole and Driver²⁴⁵⁸), amalgam dental fillings (Traub and Holmes²⁴⁵⁹), in a woman, by the husband's mustache wax (J. M. Mitchell); poison ivy (F. Wise); orange juice and tomato juice (R. S. Weiss, Urbach), mango rind (Kirby-Smith), tincture of krameria (F. Musger). In cheilitis it is sometimes necessary to apply the patch test directly on the lips, since the hypersensitiveness is not infrequently localized.

According to Hopkins,²⁴⁶⁰ *herpes simplex* repeatedly occurs in some individuals after they eat foods to which they are hypersensitive. In addition, many patients attribute outbreaks of aphthae to certain foods, particularly chocolate and nuts. However, herpes and aphthae can hardly be considered allergic reactions, but in Hopkins' opinion, it is possible that such reactions predispose the patients to invasiveness by viruses which they harbor.

Contact stomatitis is becoming increasingly frequent, owing to the use of plastic dental plates (Rattner,²⁴⁶¹ Cole and Driver²⁴⁵⁸). The chronic inflammation resulting from mucosal hypersensitiveness to plastics may be recognized as a fiery red area throughout the site of contact with the denture, with splotches of white that somewhat resemble in appearance a well developed case of chronic leucoplakia, but differing in that they may be wiped off by a gentle stroke with a pledget of cotton, revealing a bleeding surface. The affected area is sharply demarcated from the normal tissue. Patients have been known to wear acrylic dentures for more than a year before realizing that a reaction had occurred. (It should also be noted that dentures consisting of materials which are non-conductors of heat may give rise to a slight local rise in temperature, and thereby produce inflammatory changes in patients whose tissues are intolerant of such thermal changes.) Far less important as causes of contact stomatitis are denture

cream containing oil of anise (Loveman²⁴⁶²), tooth paste containing hexylresorcinol (Templeton²⁴⁵⁷), denture cleansers, oil of lavender (Goldman and Goldman²⁴⁶³), mouth washes (Port²⁴⁶⁴), mercury amalgam fillings (Traub and Holmes²⁴⁵⁹), copper amalgam fillings (Schwenkenbecker), chewing of poison ivy leaves (Shelmire,²⁴⁶⁴ Silvers²⁴⁶⁵), eucalyptus cough drops (Schwenkenbecker), and menthol lozenges (Port²⁴⁶⁴).

Rare instances are reported after eating of trout (Rowe²⁴⁶⁶) and gargling with sage tea (Urbach and Wiethe²⁴⁶⁴). The last-mentioned case is, as far as we know, the only one in the literature in which it was possible to demonstrate the presence of isolated or dissociated allergization as well as deallergization of the skin and mucosa. It therefore seems to merit at least brief discussion here.

The patient a woman of 55 years, had been in the habit of occasionally rinsing her mouth with sage tea. No untoward effects were ever observed until one day, after a perioritis that presumably was the predisposing factor, an inflammatory swelling and erythema of the lips and of the mucosa of the gums appeared after she had gargled with the tea. Application of a 2 per cent sage tea extract to the skin elicited a strongly positive local reaction. The same extract used on the mucous membrane of the lips evoked, after four hours a reaction consisting of erythema, edema and intense itching, the same symptoms appeared when a tampon saturated with this extract was inserted into one nostril. Fifteen minutes after the tea had been sprayed into the pharynx, the patient complained of a "scratchy feeling" and somewhat later of difficulty in swallowing. The hypersensitiveness was highly specific, being elicitable only by sage tea and not by even the most closely related plants of the same botanic species. The allergenic component was found to be the petroleum ether fraction of the essential sage oil. The skin was desensitized by systematic application of sage tea in gradually increasing concentrations (0.1 to 2 per cent); the mucosa, however remained sensitive. Several weeks later, a series of systematic rinsings of the mouth with gradually increased concentrations of sage tea was tried, as a result of which the buccal mucosa was completely deallergized, however, by this time, the skin again gave definitely positive reactions to sage tea.

The rarity of contact stomatitis—in contrast to the high incidence of contact dermatitis—is worthy of notice. The obvious explanation is that in the former condition, the contact

²⁴⁵⁷ TEMPLETON, H. J. *Ibid.* 42: 139, 1940

²⁴⁵⁸ COLE, H. N., and DRIVER, J. R. *Ibid.* 37: 338, 1938

²⁴⁵⁹ TRAUB, E. F., and HOLMES, R. H. *Ibid.* 38: 349, 1938

²⁴⁶⁰ HOPKINS, J. G. *New York State J. Med.* 33: 23, 1938

²⁴⁶¹ RATTNER, H. *J.A.M.A.* 106: 2230, 1936

²⁴⁶² LOVEMAN, A. B. *Arch. Dermat. & Syph.* 37: 70, 1938

²⁴⁶³ PORT, T. *Deutsche Monatsschr. f. Zahnh.* 50: 877, 1937

²⁴⁶⁴ SHELMIER, B. *J. Allergy* 11: 55, 1939

²⁴⁶⁵ SILVERS, S. H. *J.A.M.A.* 114: 2257, 1941

²⁴⁶⁶ ROWE, A. *J. Lab. & Clin. Med.* 13: 31, 1927

with the excitant is brief, the agent is rapidly diluted by the saliva, and the buccal mucosa possesses naturally strong powers of resistance and an unusually good blood supply.

Experimental investigations of the past few years have revealed the fact that allergic tests can be performed on the mucosa of the mouth in the same manner as on the skin. Goldman and Goldman⁷³² devised a standardized contact testing method employing a rubber suction cup, as an aid in the diagnosis of stomatitis venenata. The same technic has been used to ascertain contact sensitiveness to nickel and procaine hydrochloride. According to Blau rock,²⁴⁹⁷ the buccal mucosa is fundamentally capable of reacting to tuberculin and trichophyton in precisely the same way as the epidermis and the cutis, however, the allergic reactions manifested by the mucosa are in some respects different from those of the outer skin, in that they are usually of shorter duration and somewhat less severe.

Riess, Bircher, Urbach, and Delbeck succeeded in demonstrating that specific inflammation of the buccal mucosa can be elicited in an organism predisposed to dermatitis. Thus Bircher, whose skin reacted to primrose with a papulovesicular dermatitis, reported that stroking of his buccal mucosa with a primrose extract evoked a reaction consisting of acute edema, erythema, and formation of papules and vesicles, as well as distressing subjective symptoms. Urbach was able to elicit similar although somewhat less severe manifestations in patients suffering from dermatitis due to asparagus and lemons, respectively. Delbeck achieved the same results in cases with cutaneous hypersensitiveness to balsam of Peru, potassium iodide, paraphenylenediamine, atropine, and rubber. Similarly, in patients with cold urticaria, Duke¹⁵⁶⁷ was able to evoke swelling of the lips and tongue by application of ice. For a discussion of angioneurotic edema of the tongue, uvula, etc., the reader is referred to page 758.

In occasional instances, *glossitis* is also caused allergically by either drugs or foods. The so-called "allergic tongue" was found by Clem²⁴⁹⁸ to be the first manifestation of hypersensitiveness in 3 of 100 allergic children. It

consists of "hive-like" bald areas of circinate configuration with slightly raised reddish borders, occurring usually on the edges or tip of the tongue. In later years it frequently becomes a geographic tongue.

Finally, Gutmann²⁴⁹⁹ reported a case in which the patient complained of intense retrosternal pain all along the esophagus after ingestion of strawberries. A patient of Withers²⁵⁰⁰ had periodic attacks of difficulty in swallowing, when certain foods were excluded from the diet, the symptoms failed to appear. However, it was not possible to determine definitely whether the obstructive symptoms were caused by spasm or by edema of the esophageal mucosa. In this connection, the work of Harten and his associates²⁵⁰¹ is of interest in showing that absorption of unaltered protein may occur through the mucous membrane of the esophagus in rhesus monkeys.

2 STOMACH (ALLERGIC GASTROPATHY)

First of all, it should be clearly stated that the symptoms to be described here are in themselves not characteristic of gastro-intestinal allergy; they may be considered so only if accompanied by other allergic manifestations and if the results of elimination and re-exposure tests confirm this diagnosis. Clinically, acute and chronic types have to be distinguished.

Typical of the former is the so-called acute gastric crisis, appearing in anaphylaxis, and characterized by vomiting, diarrhea that is often bloody, violent epigastric and abdominal pains, and circulatory collapse. The pain is sometimes so exceptionally severe, piercing, and peritonitis like as to justify the designation of abdominal migraine. Objectively, however, there is rarely anything to be observed aside from a sometimes very marked tenderness on palpation. Not infrequently, bronchial asthma or urticaria will develop. In short, the picture is one of general shock, with the gastro-intestinal tract particularly affected. Such severe instances have been observed not only in cases of nutritive allergy—for example, following ingestion of pork (Eggston) and duck (R. Gutmann)—but also in cases of hypersensitiveness to drugs such as arsphen

²⁴⁹⁷ BLAUROCK, G. Deutsche Zahnärztliche Wochenschr. 33: 701, 1930.

²⁴⁹⁸ CLEM, N. W. Ann. Allergy 3: 1, 1945.

²⁴⁹⁹ GUTMANN, R. A. Presse méd. 40: 1654, 1932.

²⁵⁰⁰ WITHERS, O. R. South. M. J. 32: 838, 1939.

²⁵⁰¹ HARTEN, M., GRAY, I., LIVINGSTON, S., and WALTER, M. J. Lab. & Clin. Med. 27: 54, 1941.

amine (Toschkoff) and phenolphthalein (Urbach), as well as after injections of serum (Schorer), particularly tetanus antitoxin, and after allergic tests with too strong protein extracts (van Leeuwen).

While the attacks are going on, the patient generally has severe malaise. He is weak, uneasy, and apprehensive. His face is pale, his skin is cool and often covered with cold perspiration, and he commonly complains of headache and palpitation. In some instance the symptoms assume the proportions of a severe collapse. These systemic disease manifestations obviously represent varying degrees of allergic shock, and may be attributable principally to dilatation of the capillary vessels of the abdominal organs.

In less severe cases there is nausea and vomiting, the abdomen often seems to be distended, and the abdominal muscles are rather tense. While there is no particular area tender to palpation (except possibly the region of the stomach), the patient usually complains of a strange indescribable feeling of apprehensiveness in the abdomen. Suspicious symptoms of gastro-intestinal allergy include flatulent or somewhat painful indigestion which does not readily fit into any known classification of organic disease, as well as a certain amount of mental depression, dullness, and drowsiness. In some cases colicky pain dominates the picture, and, from two to four hours after ingestion of the allergen, diarrhea with mushy or watery and, in rare instances, bloody stools appears. After each defecation of this kind, there is a marked lessening of the distressing sensations in the abdomen, notably the pain usually ceases for a while, until, within about three to nine hours, the entire attack definitely comes to an end.

These conditions have also been studied roentgenologically. For this purpose, Wiedemann,²⁵² Hansen and Simonsen,²⁵³ and Hansen²⁵⁴ had their patients take the allergen together with a contrast medium, and then observed the effect on the stomach fluoroscopically. In this manner it was seen that swallowing of the mixture was immediately followed by signs of motor unrest of the

stomach, by roughening of the mucosal pattern, greatly increased peristalsis, signs of hypersecretion, spastic closure of the pylorus, and subsequent protraction of emptying time. Similar roentgenologic observations have been reported by Hampton²⁵⁵ and Urbach²⁵⁶ (Figs. 300, 301). According to Fries and Mogil,²⁵⁷ the most frequent effects of adding the specific offending food to the barium meal are gastric hypotonicity and delayed emptying time. The latter is thought to be caused by some occlusion due to edema of the pyloric mucosa, and possibly to gastric atony and pyloric spasm. While the roentgen findings are not necessarily pathognomonic, their presence should suggest the possibility of allergic gastro-intestinal disturbances, particularly when other allergic manifestations are present. These authors warn against the use of proprietary barium mixtures containing flavoring or emulsifying agents, which are commonly allergenic and may produce alterations in the roentgenograms of allergic individuals.

Far more common, however, are cases presenting chronic gastric symptoms. These include relatively mild noncharacteristic manifestations, such as belching, pyrosis, a feeling of epigastric fullness or pressure, and other symptoms of gastralgia. It must always be borne in mind, however, that these symptoms may be regarded as manifestations of an underlying allergy only when they disappear after a given food or drug has been eliminated, or when they are controlled by administration of specific propeptans (see p. 217), and when they reappear following re-exposure to the suspected agent.

A somewhat more severe syndrome, observed especially in young children, consists of regional spasms of the cardia and pylorus; these symptoms are not infrequently of allergic and particularly of nutritive-allergic origin. Thus, McCarthy and Wiseman²⁵⁸ described 6 cases of pylorospasm in infants, in all of whom the condition was found to be due to milk. The results obtained in such cases by an injection of epinephrine or by propeptan administration

²⁵² HAMPTON, S. F. *J. Allergy* 12: 379, 1941.

²⁵³ URBACH, E. *Med. Klin.* 39: 1683, 1934.

²⁵⁴ FRIES, J. H., and MOGIL, M. *J. Allergy* 14: 310, 1943.

²⁵⁵ MCCARTHY, M. P., and WISEMAN, J. R. *M. Woman's J.* 44: 333, 1937.

²⁵² WIEDEMANN, H. *Zuschr. f. aerztl. Fortbild.* 18: 630, 1921.

²⁵³ HANSEN, K., and SIMONSEN, M. *Roentgenpraxis* 9: 145, 1937.

²⁵⁴ HANSEN, K. *Deutsche med. Wochenschr.* 67: 197, 1941.

will serve to confirm or rule out the diagnosis of an underlying hypersensitiveness.

Paviot and Chevallier²²⁹ made gastroscopic examinations on patients suffering from allergic gastropathy. Following provocation of symptoms by administration of the allergen they observed the appearance of transitory edema of the mucosa localized partly in the distal portion and partly in the lesser curvature. In other instances there was mucosal bleeding or small evanescent erosions. Pollard and Stuart²³⁰ confirmed these findings and also noted thickening of the rugal folds, diminished peristalsis, secretion of grayish mucus and

due to frequently renewed action of the allergen develop chronic gastritides that heal very slowly even if the excitant is strictly excluded from the diet. Hansen estimated that about 20 to 30 per cent of all gastritis is of the allergic type due chiefly to food. Diehl described a case of eosinophilic gastritis that in his opinion was of allergic origin and possibly attributable to hypersensitiveness to tobacco.

Also to be included here is vomiting particularly the periodic vomiting sometimes observed in adults (Eiselsberg²³¹) and in older children (Fries and Jennings²³²). But even in



FIG. 300 X-RAY PICTURE OF STOMACH SHOWING EXCESSIVE SECRETION OF GASTRIC JUICE RESULTING FROM HYPERSENSITIVENESS TO LOBSTER

nodulation of the mucosa. These changes are at first reversible but after repeated attacks they may become irreversible and produce permanent damage to the mucosa.

On the basis of roentgenologic mucous membrane studies Hansen²³³ reported that allergic gastritis is essentially an angioneurotic edema of the gastric mucosa. The symptoms are the same as those observed in gastritis due to other causes. While in acute cases the mucous membrane changes ultimately disappear completely, those of long duration



FIG. 301 SAME PATIENT IN SYMPTOM FREE STATE (NORMAL SILHOUETTE)

infants the possibility of an allergic condition must be considered when there is repeated vomiting. Sales and Verdier reported the case of an infant 12 days old who was being brought up on the bottle when he was changed to the mother's breast he vomited regularly after each nursing; the regurgitation ceased when he was returned to cow's milk. These French authors succeeded in passive transfer of the hypersensitiveness to a guinea pig by means of the infant's blood. However, the present writers are by no means prepared to

²²⁹ PAVIOT J. and CHEVALLIER R. *J. de méd. de Lyon* 17: 31, 1936.

²³⁰ POLLARD H. M. and STUART G. J. *J. Allergy* 13: 467, 1942.

²³¹ EISELSBERG K. P. *Med. Abn.* 29: 1304, 1935.

²³² FRIES J. H. and JENNINGS K. C. *J. Pediat.* 17: 458, 1940.

state that the majority of cases of cyclic vomiting are of allergic origin

It is also of interest to note the relationship between migraine and vomiting. As is well known, migraine patients not uncommonly stress the vomiting of bile when describing their symptoms. Oriel²³¹ advanced the following family tree as evidence of the interrelationship between cyclic vomiting and migraine: great-grandmother, migraine; grandmother, migraine in early life, later asthma, father, cyclic vomiting, migraine, and hay fever in childhood, later asthma; patient, cyclic vomiting. Balyeat²³² described the family history of a child whose ancestors consistently had migraine and dermatitis, but who himself had suffered from cyclic vomiting for many years; after puberty, this symptom disappeared, but was replaced by a typical migraine. The vomiting in cases of hypersensitiveness to some food is probably due to disturbed peristalsis of the stomach or small intestine.

It is often more difficult to uncover the allergic origin of chronic epigastric pain. The true nature of these complaints can be ascertained only when they appear in association with other allergic symptoms (e.g., urticaria), or when they occur in a fixed relationship to certain circumstances—e.g., regularly during the asparagus or the strawberry season, or after taking aspirin, or only during the course of insulin treatment (Williams²³³), or invariably after injections of arsphenamine. In the absence of any such indications in the personal history, the physician is naturally inclined to suspect a peptic ulcer because of the chronicity of the pain—all the more so when there is hematemesis.

It might be worth mentioning here that the ulcerations of the gastric mucosa produced experimentally in allergic animals have served as the basis for the anaphylactic theory of the origin of gastric and duodenal ulcers in human beings (Ivy and Shapiro,²³⁴ Knepper²³⁵). The question as to whether an ulcer of the stomach or duodenum can be caused exclusively by an allergic condition is still a highly controversial one, and has in no way been

answered satisfactorily (Ehrenfeld²³⁶). Gay²³⁷ and Hansen²³⁸ expressed the opinion that about 20 to 30 per cent of all ulcer cases are of this origin and can be cured by elimination of the allergenic food items from the diet. Kern and Stewart²³⁹ stressed the fact that allergic manifestations were reported in either the personal or the family histories of 50 per cent of their patients suffering from peptic ulcers. Vallone²⁴⁰ suggested the possibility that ulcerations produced in the human stomach in the course of an anaphylaxis might constitute a *locus minoris resistentiae*, and that a real ulcer might form here as a result of the action of the gastric acid or pepsin.

If the theory that ulcers may be of allergic origin is correct, it will necessitate a fundamental change in the customary ulcer diet, particularly if the patient is found to be allergic to milk, egg, or wheat. There is another relationship between peptic ulcer and allergy: undigested or inadequately digested protein is absorbed through the ulcerated mucous membrane, and is thus capable of allergizing the organism (Lortat-Jacob).

Lastly, some few cases of hematemesis probably also belong to this category. In this connection, it must be remembered that experimental anaphylaxis is capable of producing hemorrhagic manifestations in both the stomach and intestines (Auer²⁴¹, Manwaring, Beattie, and McBride²⁴²). Hurst²⁴³ observed gastric hemorrhage following ingestion of tablets of acetylsalicylic acid (aspirin). Recognition of these facts may sometimes serve to clarify the pathogenesis of certain cases of gastric bleeding of obscure origin, such as those reported by Sante²⁴⁴ and by Gutmann and Demole²⁴⁵.

Gastro-intestinal allergy is not uncommonly associated with cutaneous manifestations, such as erythemas, urticaria (Fig. 302), angioneurotic edema, and pruritus. Furthermore, conjunctivitis, rhinopathy, and asthma may

²³¹ ORIEL, G. H. Allergy. London: Bale & Danielson, 1932.
²³² BALEYAT, R. Migraine. Philadelphia: Lippincott, 1933.

²³³ WILLIAMS, J. R. J.A.M.A. 91: 1112, 1930.

²³⁴ IVY, A. C., and SHAPIRO, P. F. Arch. Int. Med. 38: 237, 1926.

²³⁵ KNEPPER, R. Virchows Arch. f. path. Anat. 296: 364, 1935.
²³⁶ EHRENFELD, J. J. BROWN, A., and STURTEVANT, M. J. Allergy 10: 342, 1929.

²³⁷ GAY, L. P. J. Missouri M. A. 34: 332, 1931.

²³⁸ KERN, R. A., and STEWART, S. G. J. Allergy 3: 51, 1931.

²³⁹ VALLONE, D. Arch. ital. di chir. 25: 555, 1930.

²⁴⁰ ACEA, J. J. Pharmacol. & Exper. Therap. 19: 255, 1922.

²⁴¹ MANWARING, W. H., BEATTIE, A. C., and MCBRIDE, R. W. J.A.M.A. 80: 1457, 1923.

²⁴² SANTE, L. R. Am. J. Roentgenol. 21: 144, 1929.

²⁴³ GUTMANN, R. A., and DEMOLE, M. J. Bull. et mém. Soc. méd. d. hop. de Paris 48: 576, 1932.

also occur in conjunction with the gastric symptoms

3 INTESTINES (ALLERGIC INTESTINOPATHY)

Posselt in 1909 was one of the first to call attention to the relationship between allergy and certain intestinal disturbances of the character of colica mucosa (this term according to von Bergmann is preferable to mucous colitis) as well as certain paroxysmal secre-

association with anaphylaxis in human beings and animals. The outstanding characteristic of allergic intestinal disease is the high eosinophil cell content in the stool. This often served at a time when the pathogenesis of the condition was not understood as the basis of clinical terminology reflected in designations such as eosinophilic intestinal catarrh (Staeubli) and eosinophilic proctitis (Neubauer and Staenbl). Both of these disease



FIG. 302. GENERALIZED URTICARIA DUE TO CITRUS FRUITS AND APPEARING ONLY DURING ATTACKS OF ACUTE GASTRITIS

tory disturbances of the intestines associated with severe spasm. He went so far as to speak of intestinal asthma. In this connection it is interesting to consider the cases reported by Hurst and J. Bauer in which bronchial asthma and colica mucosa were present concurrently and particularly one of Hurst's in which the two conditions alternated. But it was the clinical and experimental investigations of Schittenhelm and Weichardt that first proved the allergic nature of enteritis occurring in

pictures are now included among the intestinal diseases of allergic etiology.

The symptoms vary considerably depending largely on the part of the intestinal tract chiefly involved in a given case (small intestine, large intestine, rectum).

The manifestations of abdominal allergy appear either as more or less severe attacks at varying intervals or as a long lasting chronic condition. The acute attacks may differ in intensity. Laroche, Richet, Jr. and Saint

Girons²⁵⁰⁶ called the very severe ones *grande anaphylaxie alimentaire*. This is characterized by violent paroxysms of intense abdominal pain, and often by severe diarrhea and shock-like symptoms. In some instances the picture may simulate peritonitis following perforation, and has therefore occasionally led to unnecessary surgical intervention (Rodén²⁵²⁷). Rowe²¹⁰ stressed the point that allergic reactions can cause moderate fever and leucocytosis with a count of from 12,000 to 18,000 leucocytes per cubic millimeter.

Pertinent to these observations is the unusual condition of benign paroxysmal peritonitis described by Siegal²⁵²⁸ and characterized by abdominal pain, fever, chills or chilliness, prostration, nausea, vomiting, belching, and constipation, but never diarrhea. Abdominal tenderness, both direct and rebound, is invariably present. Eosinophilia is noted in some patients between attacks. The condition may recur at intervals of one week to six months for many years without impairment of general health. Injection of the subserosal vessels of the visceral peritoneum in the lower abdominal cavity was noted in one case at operation. It is suggested that benign paroxysmal peritonitis is of allergic etiology, despite the facts that skin tests and elimination diets failed to incriminate specific foods, and that antiallergic therapy was not uniformly efficacious.

Hanhart¹⁰⁷³ described attacks of abdominal pain, associated with intense meteorism, due to hypersensitiveness to beef. In other cases, the clinical picture is more that of an ileus resulting from intussusception. Ratner²⁵²⁹ states that allergic enteral involvement may not merely resemble intussusception, but may actually produce the pathologic condition in irreversible form, thereby requiring surgical intervention. All transition phases from moderate to the most intense colicky pain are seen; moreover, severe diarrhea may also occur. In cases in which the last-mentioned symptoms do not appear, the findings so closely resemble those of intestinal obstruction that the

physician is likely to recommend surgery. Certain patients suffer more or less severe pain in the right iliac fossa, sometimes followed by vomiting, thus presenting a picture approximating that of appendicitis. Lastly, the condition may simulate a gastric or peptic ulcer.

SMALL INTESTINE

When the ileum is predominantly involved, the clinical picture consists essentially in colicky pains and diarrheal stools containing blood and mucus. Vomiting is also frequent. Moreover, purpura may simultaneously develop on the skin. The manifestations may be so acute, so violent and severe, that they simulate an intussusception (ileus), mesenteric thrombosis with infarction, appendicitis, or regional ileitis. According to Kaijser,²⁵³⁰ an allergic reaction of the small intestine presents the following findings, as actually observed in the course of laparotomies: the peritoneal cavity usually contains a clear serous liquid that is likely to be bloody in severe cases, notably in those in which there are hemorrhages from the intestinal mucosa. The affected intestinal loops, which may vary considerably in length, are markedly swollen and usually exhibit a glassy subserous edema. Furthermore, the involved portion is more or less erythematous and often marked by inflammatory mucosal infiltration that is usually rich in eosinophile cells, and by subserous hemorrhages of varying size and number. The edema also extends into the mesentery. Thus, severe cases present a picture resembling that of true intestinal infarction, and the main clinical difference between the two is, as Gregoire²⁵³¹ pointed out, that the former clear up spontaneously. In other instances, the circumstances observed during laparotomy simulate those of a phlegmonous enteritis or regional ileitis.

In a case of the delayed type of food allergy reaction reported by Hampton and Cooke²⁵³² there was noted abnormal segmentation of the small intestine following a barium meal containing the allergen. Wing and Smith²⁵³³

²⁵²⁸ LAROCHE, G., RICHEL, C., JR., and SAINT-GERONS, F. *Allimentary Anaphylaxis* (transl. by Rowe, M. P., and Rowe, A. H.) Berkeley, Calif. Univ. Calif., 1939.

²⁵²⁹ RÖDÉN, S. *Nord med tidnkr* 15, 592, 1937.

²⁵²⁸ SIEGAL, S. *Ann Int Med* 23, 1, 1945.

²⁵²⁹ RATNER, B. *J.A.M.A.* 127: 696, 1945.

²⁵³⁰ KAIJSER, R. in KALLIÖ, P. (ed.) *Fortschritte der Allergiehehre*. Basel, Karger, 1939, *Arch. f. klin. Chir.* 183, 36, 1937.

²⁵³¹ GREGOIRE, R. *Mém. Acad. de chir.* 63, 930, 1937.

²⁵³² HAMPTON, S. F., and COOKE, R. A. *Ann Int Med* 16-11, 1942.

²⁵³³ WING, W. M., and SMITH, C. A. *J. Allergy* 14, 56, 1942.

studied 9 patients suspected of having gastrointestinal allergy, and in 3 found roentgenologic changes of such a degree that they could not be explained as due to the nutritive food value but were thought to be the consequence of specific allergic reactions. These changes consisted of dilatation of the jejunal loops, segmentation, and altered motility, and were suggestive of those of a deficiency state. Fries and Mogil²⁵⁰⁷ also observed increased segmentation in some of their cases, and, in rare instances, accelerated motility of the small intestine, although these results occurred less frequently than abnormalities in the gastric findings.

Gregoire²⁵¹¹ and Kaiserling and Ochse²⁵¹² claim that they were always able to elicit a local allergic reaction in the intestines of sensitized animals by a local injection of the specific allergen. However, the results of these investigations have in part been disputed by Kiang,²⁵¹³ while Wing and Smith²⁵¹⁴ observed no significant alteration in the small bowel pattern of sensitized guinea pigs during anaphylaxis.

Gray, Harten, and Walzer²⁵¹⁵ studied the allergic reactions of the passively locally sensitized mucous membranes of the ileum and colon in 2 patients, one of whom had an ileocolostomy and the other a colostomy. The allergic reactions were induced by administration of the specific allergen orally, by introduction into the lumen of the bowel, or by application directly to the sensitized area. The allergic responses, which developed within five to eight minutes in the sensitized mucosal sites, were characterized by edema, hyperemia, and excessive secretion of mucus. In experiments on monkeys, Walzer and his associates²⁵¹⁷ studied the effects of intravenous administration of the antigen: the injection was followed, within about one minute, by pallor and edema of the passively locally sensitized mucous membrane of the ileum, cecum, or stomach, as well as by hyperperistalsis and

spasm. Walzer²⁵¹⁸ however, refutes the concept that the smooth muscle is the shock tissue in allergic reactions of the alimentary tract. On histologic examination, the epithelial cells of the mucous membranes did not appear to be materially affected. It was found that most of the changes had occurred in the connective tissue beneath the lining surfaces.

There is evidence that some cases of chronic enteritis are of allergic origin. This is especially to be thought of when the usual medical regimen fails to help, or when a bland diet, including particularly milk, wheat, and egg, is followed by an increase in symptoms. Elimination of the suspected foods or preprandial administration of the propeptans will rather quickly show whether an allergic mechanism is operative.

McKhann, Spector, and Meserve²⁵¹⁹ found evidence of gastro intestinal allergy in 4 cases of celiac disease, although it was not clear whether the allergy was secondary to the celiac syndrome or vice versa.

COLON

While it is difficult sometimes to distinguish clinically whether in a given case the small or large intestine or both are affected, there are quite a few instances in which operation or X-ray studies revealed a predominant or exclusive involvement of the colon.

The symptom complex is dominated by pain and spasms and these may also lead to incorrect diagnoses and unnecessary surgical intervention. When the spasms are of such intensity as to reach alarming proportions it is easy enough to understand that they may readily be misinterpreted and lead to erroneous diagnoses. As a matter of fact, this condition has been responsible for needless operations for presumed duodenal ulcer, appendicitis, or cholecystitis. Thus, R. Gutmann reported a patient who had painful crises of such severity and suddenness, together with vomiting and abdominal distention, that she had been subjected to no less than four operations within a few years—viz., on the ovaries, adnexae, appendix, and gallbladder. Needless to say, the operations were of absolutely no

²⁵⁰⁴ KAISERLING H. and OCHSE W. *Vierteljahrsschr. f. path. Anat.* 298: 177, 1935.

²⁵⁰⁵ KIANG T. S. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 95: 227, 1939.

²⁵⁰⁶ GRAY I., HARTEN M. and WALZER M. *Ann. Int. Med.* 13: 2050, 1940.

²⁵⁰⁷ WALZER M., GRAY I., STRAUS H. W. and LIVINGSTON, S. *J. Immunol.* 34: 91, 1938.

²⁵⁰⁸ WALZER M. *J. Lab. & Clin. Med.* 26: 1867, 1941.

²⁵⁰⁹ MCKHANN C. F., SPECTOR S. and MESERVE E. R. *J. Pediat.* 22: 362, 1943.

benefit in this case, and the patient was not cured until peptone therapy was instituted. It should be noted that these forms of intestinal allergy are distinguished by the absence of diarrhea. In another case, reported by Efron,²⁵⁰ the patient was repeatedly rushed to a hospital because of symptoms suggesting intestinal obstruction. Each time, however, there was a marked improvement before operation had definitely been decided upon. At last it was discovered that the condition was attributable to hypersensitiveness to wheat; experimental ingestion of white bread sufficed to bring on intestinal obstruction.

Far less fortunate, at least in the beginning, was the patient reported on by M. Gutmann,¹⁰² who underwent seven emergency operations within six years because his symptoms strongly suggested an ileus; it was finally found that the intestinal spasm was due to hypersensitiveness to the yeast in beer, and appropriate therapeutic measures for this met with complete success. X-ray examinations made at the height of the attacks of pain in such cases revealed colonic spasms; after an injection of epinephrine, these literally vanished from the fluoroscopic screen (Eyermann²⁵¹). Gay²⁵² presented roentgenologic evidence of spasm and irritability of the colon during the attack in a patient with acute allergic abdomen. Hypertonicity of the transverse and descending colon was noted by Fries and Mogil²⁵³ in a few of their cases after a barium meal containing the specific allergenic food. Rectal instillation of allergen-barium mixtures produced similar changes or, rarely, dilatation.

In a number of cases in which laparotomy was performed because the patients complained of severe pains, it was found that the intestinal walls presented edematous swelling with an appearance similar to that described above in reference to the small intestine (Kajiser²⁵⁴). Moreover, Kaiserling and Ochse,²⁵⁵ in their animal investigations, discovered conditions analogous to those observed in the human small intestine.

Another form—"irritable colon" or mucous colitis—is characterized by excessive secretion of mucus from a membrane that does not

manifest much inflammation. The clinical picture is dominated by mucous diarrhea, frequently accompanied or followed by spastic constipation. The intestinal mucus has a high eosinophile cell content in the allergic type, and Charcot-Leyden crystals are also to be found when the stool is permitted to stand in the laboratory for some time or when the mucus has remained in the intestine longer than usual. In severe cases, entire portions of the intestinal mucosa are sloughed off (membranous colitis). Further symptoms and signs are abdominal cramps aggravated when peristalsis is increased, distention, a tender and palpable sigmoid colon, and only slight mucosal changes in the rectosigmoid when examined sigmoidoscopically. Mucous colitis may occur without abdominal pain.

Numerous authors, including Richet, Vaughan, Rowe, Eyermann, and Hollander, have reported on mucous colitis due to allergy to some food. Particularly interesting is the observation reported by Hecht and his associates²⁵⁶ on hypersensitiveness to the tetrabromofluorescein in lipstick as a cause of this disease. In a known milk-sensitive patient with intestinal disturbances of the nature of mucous colitis, Epstein²⁵⁷ observed that control of an associated hyperthyroidism led to complete relief of the intestinal symptoms. Grimm traced one case to inhalation of dust from books, and in this connection it might be well to note the animal experiments of Lehman with copper dust, showing that the greater part of the inhaled dust is retained chiefly in the gastro-intestinal tract and not in the lungs. However, the writers would like to stress at this point that, in their opinion, only a minority of cases of mucous colitis are of allergic origin. Among other causes are direct irritants (coarse foods, cathartics, infections of the colon), instability of the autonomic nervous system, systemic infectious diseases, sudden weight loss, and above all, emotional tension and functional neurogenous factors.

Within the past few years attempts have also been made to attribute chronic ulcerative colitis to allergy. This viewpoint has been championed chiefly by Andresen,²⁵⁸ who demon-

²⁵⁰ EFRON, B. G. *New Orleans M & S J* 84: 540, 1931.

²⁵¹ EYERMANN, C. H. *J Missouri M A* 24: 129, 1927.

²⁵² GAY, L. F. *ibid* 31: 385, 1934.

²⁵⁶ HECHT, R., KAPPAPORT, B. Z., and BLOCH, L. *J.A.M.A.* 113: 2110, 1939.

²⁵⁸ ANDRESEN, A. F. R. *Am J Digest Dis & Nutrition* 9: 91, 1942.

strated food allergy to be the etiologic factor in two thirds of his cases. While skin testing with food extracts was of no aid, elimination diets revealed that milk was the chief offender (in 84 per cent of the cases) and that wheat, tomatoes, oranges, potatoes, and eggs (in from 18 to 9 per cent of the cases in the order named) were less important allergens. Rowe²⁵⁴⁵ also indicated that chronic ulcerative colitis might in some cases be caused primarily by allergy and secondarily by superimposed infection and the effects of resultant avitaminosis. Milk again headed the list of offending foods, and a cereal, milk, and fruit-free diet resulted in symptomatic relief in the majority of cases. Most authorities are of the opinion, however, that allergic factors represent the principal cause in no more than 10 per cent of cases, and that in another group of about equal size, hypersensitiveness to some food is a minor factor in the production of symptoms. (Bargen, Ballinger.) Bargen²⁵⁴⁶ points out that while mucosal abrasions with resulting ulcers of a transient nature may occur in severe cases of intestinal allergy, this should be considered as a condition quite apart from the problem of ulcerative enterocolitis. The great majority of cases of the latter are due to streptococcal, tuberculous, or amebic infection, or represent a late phase of bacillary dysentery, or are associated with lymphopathia venerea, or, as more recent investigations have shown, are part of a deficiency state.

According to Bockus²⁵⁴⁷ chronic regional or cicatrizing enteritis, like ulcerative colitis, may predispose to sensitivity to certain foods. Intolerance to milk may be noted in some patients during the active phase of the disease, and in others with extensive involvement. He holds that while the disease is not of allergic etiology, allergy may be responsible for exacerbations of symptoms and perhaps for conditioning the chronicity of the lesion.

Intestinal hemorrhages have also been observed as the principal expression of an allergic reaction. Thus Habermann reported the appearance of such hemorrhages together with urticarial skin manifestations as resulting from hypersensitiveness to acetylsalicylic acid.

Henderson²⁵⁴⁸ observed melena and pain in an allergic individual after ingestion of banana. Rubin¹⁹⁸¹ described a clinical syndrome in infants between 3 and 5 weeks of age who had acquired an allergy to cow's milk; the symptoms consisted of intestinal bleeding together with colicky pains and frequent mucus-containing stools. The melena, along with the other intestinal disturbances, disappeared within a few days after milk was eliminated from the diet.

Mention should also be made here of the passing of bloody stools, which together with recurrent attacks of purpura of the skin, acute abdominal pain, urticaria, angioneurotic edema, and joint manifestations are characteristic of the symptom complex known as Henoch's disease or purpura abdominalis. It was Osler²⁵⁴⁹ who in 1914 first suggested the possibility of an underlying allergy because of the commonly observed association of these cutaneous symptoms with visceral and joint manifestations. He further reported the finding in the course of operations of localized areas of edema in the bowel wall. Glanzmann²⁵⁵⁰ expressed belief in a bacterial allergic origin. However, definite proof of the potentially allergic nature of Henoch's purpura was furnished by Duke⁵⁰⁰ (1 case), Alexander and Evermann²⁵⁵¹ (9 cases), and Bisson and David²⁵⁵² (1 case); these authors succeeded in producing the characteristic abdominal pain, purpura, and angioneurotic edema by means of ingestion of the suspected food, and in relieving these symptoms by withholding this food.

Similar cases have since been reported by other authors; the majority were due to hypersensitiveness to food, the minority to drugs to parenterally administered substances (e.g., serum injections), to intestinal worms, and to bacterial antigens. Quite a few emergency operations have been performed for Henoch's purpura associated with acute abdominal pain (Althausen and associates²⁵⁵³). Particularly difficult from the differential diagnostic stand-

²⁵⁴⁸ HENDERSON A. T. *Canad. M. A. J.* 44: 33, 1941.

²⁵⁴⁹ OSLER W. *Brt. M. J.* 1: 517, 1914.

²⁵⁵⁰ GLANZMANN E. *Jahrb. f. Kinderh.* 83: 271, 1916.

²⁵⁵¹ ALEXANDER H. L. and EVERMANN C. H. *J. A. M. A.* 92: 2852, 1929.

²⁵⁵² BISSON C. and DAVID P. *Lyon méd. du Canada* 73: 873, 1941.

²⁵⁵³ ALTHAUSSEN T. L., DEANER W. C., and KERR W. J. *Ann. Surg.* 105: 242, 1937.

²⁵⁴⁴ ROWE A. H. *Ann. Int. Med.* 17: 83, 1942.

²⁵⁴⁵ BARGEN J. A. *J. A. M. A.* 126: 1009, 1944.

²⁵⁴⁶ BOCKUS H. L. *ibid.* 127: 449, 1944.

point are those rare cases in which Henoch's purpura is more or less confined to the internal organs without cutaneous manifestations (Hadley). Pratt's statement²⁵⁴ on the subject is well worth quoting: "No one should operate on a child with abdominal colic until the diagnosis of Schoenlein-Henoch's disease has been excluded."

Another group of patients present rather mild but nevertheless distressing symptoms that are often labeled dyspepsia, nervous indigestion, and even intestinal toxemia. As Alvarez²⁵⁵ pointed out, these patients often complain of flatulence, abdominal distention, and crampy pain. It is worth while remembering that often it is not the supposedly indigestible foods that are the gas producers, but rather those usually considered innocuous, such as milk and egg.

APPENDIX

The literature contains reports on a number of cases in which the clinical picture of allergic gastro-intestinal attacks so closely simulated that of appendicitis that an operation was either seriously considered or actually performed. Thus, Wise and Sulzberger²⁵⁶ observed an arsenamine hypersensitivity in a young nurse, with dermatitis, asthma, and severe appendicitis-like pains, these symptoms appeared only once weekly—namely, on the day when she prepared arsenamine solutions. In one of the senior author's cases of fall hay fever, the patient had acute abdominal symptoms, suggestive of appendicitis, in the month of September in three consecutive years, these could be brought under complete control by epinephrine injections. Clog²⁵⁷ described several abdominal manifestations, resembling appendicitis, that appeared in the course of a serum exanthem. A patient who underwent an operation because of these symptoms presented marked engorgement and swelling of the mesenteric lymph nodes. Black²⁵⁸ reported a case simulating recurring attacks of appendicitis; the symptoms dis-

appeared after squash and cabbage had been eliminated from the patient's diet, but returned when the patient was induced to eat these foods again. Pelner²⁵⁹ attributes the frequency of allergic reactions in the cecal region, thereby resembling appendicitis, to the fact that the chyme rapidly reaches this point but is physiologically detained for absorption of fluid.

McIntosh²⁶⁰ claims that the not infrequently encountered discrepancy between the clinical and subjective manifestations in appendicitis-like abdominal pains on the one hand, and the pathologic findings in the course of an appendectomy, or the histologic picture presented by the resected appendix, on the other, can sometimes be explained on the basis of an allergic involvement. This conclusion, however, is permissible only when the appendix presents no acute or chronic inflammatory manifestations, and when there are large quantities of mucus as well as Charcot-Leyden crystals in the lumen, and when eosinophile cells are found in the walls. In a series of specimens studied by Dutton,²⁶¹ microscopic examination frequently revealed edema, capillary congestion, and eosinophilic infiltration; he holds these pathologic changes to constitute presumptive evidence of an allergic tissue response, which may be reversible or may pave the way for bacterial invasion with subsequent necrosis and suppuration. Wasserman²⁶² made similar histologic observations. Ratner²⁶³ subscribes to the concept that the primary spasm and wheal formation, along with the involvement of the vessels of the submucosa and serosa, may lead to such irreversible changes as gangrene and perforation. In Dutton's²⁶¹ series, there was also a high incidence of personal histories of outspoken allergic states. It is not necessary to point out that, despite these theories, appendicitis should still primarily be treated as a surgical disease.

Fischer and Kaiserling²⁶⁴ described animal experiments in which changes in the appendix

²⁵⁴ PRATT, J. H. *Anaphylactoid Purpura*. In Osler, W. (ed.) *Modern Medicine*, Philadelphia: Lea, 1927, vol. 5, p. 135.

²⁵⁵ ALVAREZ, W. C. *J.A.M.A.* 129: 21, 1942.

²⁵⁶ WISE, F., and SULZBERGER, M. B. *Ar. Bk. Dermat. & Syph.* 1934, p. 91.

²⁵⁷ CLOG, L. W. *Bull. Soc. de pédiat. de Paris* 36: 354, 1938.

²⁵⁸ BLACK, J. H. *Rev. Gastroenterol.* 8: 17, 1941.

²⁵⁹ PELNER, L. *Am. J. Digest. Dis.* 12: 17, 1945.

²⁶⁰ MCINTOSH, J. A. *South. M. J.* 23: 1147, 1930.

²⁶¹ DUTTON, L. O. *Ann. Allergy* 1: 17, 1943.

²⁶² WASSERMAN, F. cited by GREENBAUM, J. V. discussion to Ratner²⁶³.

²⁶⁴ FISCHER, E., and KAISERLING, H. *Klin. Wchschr.* 16: 1143, 1937.

were produced in sensitized rabbits by injections of the antigen into the submucous lymph spaces and claimed that these changes correspond to acute appendicitis in human beings. They attribute the sensitization of the appendix in man to a distant focus of infection such as a tonsillitis. These experiments were sharply criticized by Aschoff²⁵⁶ who attacked the concept that experimental allergic appendicitis and acute appendicitis in human beings are of identical pathogenesis.

RECTUM

Anorectal manifestations may take the form either of proctitis of rectal spasms or tenesmus or of pruritus ani. Thus LeNoir, Richet, Jr., Renard and Barreau described a case in which the patient had been suffering for six months from colic associated with diarrhea and constipation, stools containing mucus and blood and the loss of 8 pounds in weight during ten weeks. Cancer of the rectum and of the sigmoid was at first suspected but the investigations along these lines were negative. Finally the patient herself observed that the acute attacks always appeared following ingestion of raw meat or raw milk. When these foods were eliminated from her diet she no longer had symptoms but they reappeared just as soon as these foods were again consumed. Thomas and Renshaw^{256a} reported on characteristic reactions in the form of edema, erythema and vascular congestion observed proctoscopically and appearing after the application of certain allergenic substances to the rectal mucosa in patients suffering from intestinal allergy. Following a positive mucosal reaction, the patient usually experienced abdominal cramps and rectal discomfort.

Lastly an occasional case of pruritus ani may be of allergic origin. Thus Wynn^{256b}, Cohen^{256c}, Stokes^{256d}, Vaughan^{256e} and Tuft^{256f}, among others, observed cases of this kind due to food allergy. Wynn^{256b} reported pruritus ani attributable to marked hypersensitivity

to wheat. Schreus^{256g} a similar case due to tomato in which administration of specific tomato propeptans resulted in complete cure. Cohen^{256c} described 2 instances in which generalized pruritus was the only symptom of a nutritive allergy (one to pork the other to buckwheat and potatoes). According to Schapiro and Albert^{256h} elimination of the foods producing positive intradermal reactions resulted in improvement in 15 per cent of their cases of pruritus ani. Severe perianal dermatitis may follow long-continued pruritus ani (Fig. 303). The senior author was able to



FIG. 303. PRURITUS ANI DUE TO HYPERSENSITIVENESS TO MILK.

Dermatitis appeared only after many years of pruritus.

demonstrate hypersensitivity to drugs as well as to cocoa butter (theobromine) in rectal suppositories. Moreover there are instances probably more common than is today recognized in which local bacterial and fungus allergy may be the etiologic factor in this condition. In cases in which a pathologic intestinal flora is present the writers prepare an autogenous vaccine for perianal injections given in gradually increasing doses. Stroud²⁵⁶ⁱ

^{256a} ASCHOFF, L. *Ergebnisse der Medizin* 51: 144, 1915.

^{256b} THOMAS, J. W. and RENSHAW, R. J. F. *Cleveland Clin. Quart.* 8: 17, 1941. *T. Am. Poet. Soc.* 42: 306, 1941.

^{256c} WYNN, J. J. *Lab. & Clin. Med.* 13: 16, 1917.

^{256d} COHEN, M. B. *J. A. M. A.* 6: 37, 1922.

^{256e} STOKES, J. H. *Internat. Clin.* 1: 147, 1940.

^{256f} VAUGHAN, W. T. *South. M. J.* 56: 2, 1930.

^{256g} SCHAPIRO, S. and ALBERT, M. M. *J. Invest. Dermat.* 4: 29, 1942.

^{256h} SIBO, D. C. M. *J. A. Ergo* 10: 245, 1939.

reported satisfactory results from various fungus extracts.

Gray and Walzer²⁵⁷ have shown that the mucous membrane of the rectum can be sensitized passively with human antibody-containing serum. The reaction can be elicited by either oral administration or rectal instillation of the allergen. The symptoms include pruritus, a sense of fullness, and increased secretion of mucus.

B. PATHOGENESIS OF THE ALLERGIC GASTRO-INTESTINOPATHIES

A few examples will suffice to illustrate the various ways in which allergization of the gastro-intestinal tract takes place, as well as the variety of antigens that come into play (exogenous, endogenous, primary, and secondary).

Under physiologic conditions, healthy adults—not to mention children—can absorb undigested protein. In order to demonstrate this, M. Walzer¹⁸⁴ performed the following experiment. Normal subjects received intracutaneous injections of serum from individuals hypersensitive to fish (Prausnitz-Kuestner method) and then were given the same protein by mouth. The subsequent positive skin reaction at the site of the serum injection seems to prove beyond question that the normal intestine is capable—even under physiologic conditions—of absorbing undigested specific protein.

The extent to which such resorption occurs depends on whether there is a normal or diseased condition of the mucosa, as was demonstrated by Gutzeit:¹⁸⁶ small quantities of serum from a subject hypersensitive to fish were injected (Prausnitz-Kuestner technic) into both healthy subjects and patients with gastro-enteritis. Then, when the healthy subjects were given 50 cc. of a fish extract (i.e. specific antigen) through a stomach tube, there was no reaction at the site previously injected with serum. On the other hand, the gastro-enteritis patients, similarly treated, showed wheals and erythema at the prepared skin sites. However, when Gutzeit quadrupled the amount administered to the healthy individuals, they also reacted at the passively allergized skin sites.

In animal experiments, guinea pigs of any age can be allergized and shocked by oral administration of protein food (Ratner and Gruehl¹⁸⁵). Such allergization can be more quickly achieved by adding to the antigen some saponin such as glycyrrhiza (Urbach and Kitamura¹⁸⁹). The latter reduces the surface tension of the mucosa, which thereby becomes much more rapidly and extensively permeable. The experimental investigations of Hartley¹⁹⁰ indicate that guinea pigs receiving crystalline egg albumin by mouth develop antibody titers as high as those of the animals receiving the antigen parenterally. He found a definite relationship between the titer of the circulating antibodies and the severity of the anaphylactic shock following oral administration of antigen.

In the great majority of cases, gastro-intestinal allergy is a reaction to some food. According to Thomas and Wofford,²⁵⁷ milk, beans, eggs, chocolate, and wheat are the most important substances; while the list compiled by Alvarez¹⁹¹ on the basis of the statements of 500 intelligent men and women included milk, raw apples, onions, cabbage, chocolate, radishes, tomatoes, cucumbers, and eggs. In some instances, however, drugs, bacteria from foci of infection or pathologic intestinal flora, and even pollen must be taken into consideration as possible causal agents. A case reported by Duke^{257a} serves as an excellent illustration of the specificity and high degree of hypersensitivity manifested in some of these cases: the patient responded with very severe gastro-intestinal symptoms following ingestion of only one drop of honey, and indeed only of one kind of honey collected from certain plants.

The following observation by Flandin^{257b} clearly shows the significance of a sudden overloading of the digestive organs with a foreign protein. A woman 35 years of age had been living on a strictly vegetarian diet for three years; one day she suddenly decided to eat some veal and eggs, and subsequently suffered severe attacks of urticaria, edema of the glottis, and dysentery-like diarrhea. Flandin succeeded in passively transferring to a guinea pig the hypersensitiveness to meat and egg.

Quite frequently, however, the causative

²⁵⁷ THOMAS, J. W., and WOFFORD, C. F. *ibid* 8 311, 1941

^{257a} DUKE, W. W. *Ann Otol. Rhin. & Laryng.* 36, 829, 1927

^{257b} FLANDIN, C. *Bull. et mem. Soc. méd. d. hôp. de Paris* 54: 911, 1930

^{257c} GRAY, I., and WALZER, M. *Am. J. Digest. Dis. and Nutrition* 4 707, 1938

agents are secondary allergens. They comprise the digestion products of foodstuffs, their intermediary products, and even the intermediary products of drugs. Thus Urbach²⁵⁷⁶ showed that the allergen is sometimes formed only as a result of the action of pathologic bacterial flora of the intestines on ingested proteins. The discovery of this mechanism has practical therapeutic significance for in such cases we can speedily abolish the allergic symptoms by treatment directed toward altering the pathologic intestinal flora by such measures as diet, *Bacillus acidophilus* preparations, colonic irrigations, and charcoal. The fact that in these cases the causative allergen is not the food itself but rather split products formed in the intermediary processes of digestion (Cooke²⁵⁷⁷) may be the reason why skin tests with extracts of the foods themselves are so frequently negative in gastro intestinal allergies. The concept of sensitization to the derivatives of protein digestion helps to explain the delayed type of clinical reactions following ingestion of foods.

Our present knowledge in regard to the endogenous allergens is very limited. These substances originate in the organism itself but are altered by degenerative and autolytic processes and so acquire the character of foreign substances and thus of antigens. Recent studies²⁵⁷⁷ have shown however that endogenous antigens—especially those formed in the intestinal tract—play an important part in the production of gastro intestinal allergy.

Gastritis is recognized as a particularly important predisposing factor in the production of gastro intestinal allergic diseases. One encounters again and again—in the literature as well as in one's clinical experience—cases in which the consumption of some spoiled food or of some extremely hot or cold food or drink, or excessive or unaccustomed indulgence in alcohol results in gastric disturbances that in turn are followed by any of the various allergic gastro intestinal symptoms described above. It is by no means a rarity to observe a marked improvement in the allergic condition

after the eradication of the underlying gastritis and recurrence of the allergic symptoms just as soon as the gastric disturbance reappears.

Moreover intestinal allergic manifestations may result from an inadequacy of digestive juices or enzymes (Walzer and Walzer²⁵⁷⁸, Barber and Oriel²⁵⁷⁹). This also holds true in the case of children (Bray²⁵⁸⁰). Carnot and Slavu's experimental work demonstrated that oral administration of 3 per cent hydrochloric acid served appreciably to prevent anaphylactic reaction to certain weakly antigenic proteins such as horse serum. In cases of hypochlorhydria and achylia the present writers have succeeded in correcting gastro intestinal allergy by administration of large doses of hydrochloric acid and pepsin, sometimes in combination with pancreatin or with the indicated propeptans.

The observation of Hettwer and Kriz²⁵⁸¹ that an increase in intra intestinal pressure resulting from stasis hastens the absorption of protein assumes importance in view of the fact that constipation is so frequently encountered in cases of gastro intestinal allergy. The authors studied this problem by injecting horse serum into isolated loops of the intestines of guinea pigs and eliciting anaphylactic manifestations after oral or rectal administration of the protein. Anaphylactic reactions did not occur however when the horse serum was given intraperitoneally.

As to just how allergic abdominal pains are caused little is as yet known. Some authorities quite simply assume that there must be an internal urticaria or an angioneurotic edema of the intestinal mucous membrane (Rowe²⁵⁸²). On the basis of his roentgenologic investigations Eyerzmann²⁵⁸³ attributes the pain to spasm of the smooth muscle. Along with these possibilities Ratner²⁵⁸⁴ also considers spasm of the small vessels of the gastro-intestinal walls. In agreement with Shorer²⁵⁸⁵ we are inclined to assume that the combined effect of edema and spasm is necessary to cause pain of this kind; the mechanism might well consist in the pressure imposed by the smooth muscle spasm upon the edematous tissues.

²⁵⁷⁶ URBACH E. Arch. f. Dermat. u. Syph. 159: 523, 1930.

²⁵⁷⁷ Idem. Arch. Dermat. & Syph. 45: 697, 1942.

²⁵⁷⁸ WALKER A. and WALKER V. Am. J. N. Sc. 173: 279, 1927.

²⁵⁷⁹ BARBER H. W. and ORIEL G. H. Lancet 2: 1009, 1928.

²⁵⁸⁰ SCHÖBER G. Schweiz. med. W. btschr. 55: 330, 1925.

The question as to how the allergization of the intestines is produced in the first place can be answered by mentioning several possibilities, some of which have already been considered, at least briefly, in the discussion of the pathogenesis of allergic gastropathy. It should be added here that the intestines can become allergized by the penetration of undigested or inadequately digested food proteins through an intestinal mucosa that has been damaged by inflammation, erosion, or loss of mucus, and also by the presence of certain parasitic infestations, the metabolic products of the parasites bringing about a state of chronic irritation.

Moreover, the enteral route is not the only way by which allergic responses can be elicited in the intestines. Severe intestinal manifestations are part of the typical picture of experimental as well as of human anaphylaxis. When the allergen is reinjected into allergized dogs (Schittenhelm and Weichardt), theyretch violently, vomit, and pass markedly bloody liquid stools. Autopsy reveals that the intestines are filled with a liquid containing blood and mucus. Occasionally similar although somewhat less severe manifestations appear in patients with intestinal symptoms after ingestion of certain foods, when they happen to receive the same protein parenterally. Thus, Antona⁵¹⁹ reported the case of a man who always had severe gastro-intestinal symptoms on ingestion of octopus meat, and who was similarly affected by cutaneous administration of an extract of octopus. In another instance, observed by Jacquelin and Richet, Jr.,²⁵⁴¹ severe diarrhea followed ingestion of beans, and there was an identical reaction to cutaneous injection of an extract.

The precise route (whether enteral or parenteral) by which gastro-intestinal disturbances due to pollen are brought about, must be determined in each instance. Cases on record conclusively demonstrate that both routes are possible. Occasionally gastro-intestinal manifestations are elicited in hay fever patients by pollen injections. Far more commonly observed, however, are such reactions in hay fever patients following oral

administration of pollen. It should be borne in mind that specific gastro-intestinal responses can also be evoked by ingestion of natural honey, which very often contains a considerable amount of pollen. As a rule, when such disturbances appear during the grass or ragweed season, and when other evidence definitely indicates an allergy to pollen, it is justifiable to assume that the symptoms represent an intestinal hypersensitiveness to pollen. Finding of eosinophils in the stool will support this diagnosis.

C. DIAGNOSIS OF THE ALLERGIC ETIOLOGY OF GASTRIC AND INTESTINAL DISEASES

All the gastro-intestinal symptoms mentioned may be suspected of being allergic only if there are other concurrent or alternating manifestations of allergy, such as urticaria, angioneurotic edema, rhinopathy, or migraine. When none of the latter is present, it is often impossible to prove an allergic etiology.

It is frequently quite difficult to establish the differential diagnosis as between organic diseases (such as peptic ulcer, cholecystitis, or appendicitis) and functional conditions (as in certain cases of spasm of the cardia, pylorus, or colon) on the one hand, and allergic conditions of the gastro-intestinal tract on the other. The clinical pictures are often identical. The following diagnostic measures are available.

(1) There is often a personal or family history of present or previous allergic disease. This includes not only the obvious forms (e.g., urticaria, hay fever, asthma, migraine), but also such symptoms as aversion to certain foods, intolerance of certain drugs, and belching, flatulence, or a sense of pressure in the stomach after eating certain foods. Particularly suspicious is the appearance of allergic reactions in other organs simultaneously or alternately with those of the digestive tract.

(2) To reach a decision quickly as to whether pain, spasm, or some other symptom is of allergic nature, epinephrine may be administered and its effect observed.

(3) When a food is believed to be the causative allergen, an elimination diet may be tried. If this maintains a symptom-free state, trial feedings of the suspected food will frequently elicit definite information. A carefully kept

²⁵⁴¹ JACQUELIN, A., and RICHEL, C., Jr. *Compt rend Soc. de biol* 84 18, 1921.

food diary is often a useful diagnostic adjunct. Another method is institution of a specific propeptan diet.

(4) Cutaneous or intracutaneous skin tests are in general futile, they may be evaluated as positive evidence only if corresponding gastro-intestinal (i.e., focal) responses are elicited at the same time (as, for example, in the cases of Antona,⁹¹⁹ and Jacquelin and Richet⁷⁸¹). Much the same evaluation applies to the leucopenic index and pulse acceleration tests.

(5) It is advisable always to perform a fractional gastric analysis, examination of the feces, roentgenologic studies of the gastro-intestinal tract, and possibly also gastroscopy and proctoscopy. When the X ray appearance of the previously affected organs returns to normal within a few hours after administration of epinephrine, this, together with the clinical symptoms, confirms the allergic character of the case.

(6) Use of a drug suspected of being the guilty allergen should be discontinued, when the symptoms no longer appear, the drug should be intentionally administered.

(7) Allergic reactions may also be accompanied by fever, as well as by a leucocytosis with from 12,000 to 18,000 leucocytes per cubic millimeter. Moreover, in acute attacks there need be no eosinophilia whatever. But when the attacks recur over a considerable period of time, a more or less marked eosinophilia is commonly observed during the intervals of remission. The demonstration of eosinophilic leucocytes in the stool is helpful.

(8) Lintz has expressed the opinion that the absence of muscular rigidity is a constant and dependable indication in cases of abdominal allergy (and thus constitutes a definite contra-indication for operation). This view is emphatically contradicted by Gay,⁷⁴⁷ Roden,²⁸⁷ and others who occasionally observed very tense abdominal musculature.

(9) In cases of abdominal pain associated with fever, leucocytosis, and muscle rigidity, it is advisable to submit the patient to an exploratory laparotomy, unless the presence of an underlying allergy can be unequivocally demonstrated, and unless the symptoms show marked subsidence following an injection of epinephrine. On the other hand, it is surely

important for the surgeon as well as for the internist, to become "allergy conscious."

D TREATMENT OF ALLERGIC DISEASES OF THE STOMACH AND INTESTINES

The treatment of the gastro-intestinal allergies, depending on whether or not the cause can be ascertained, is specific, meta-specific, or symptomatic.

1 SPECIFIC THERAPY

If the allergen is a drug or a rarely consumed food, its use should be discontinued. But when the allergen is a food that cannot readily be dispensed with—e.g., eggs, milk, wheat—the hyposensitization or deallergization measures below may be employed. Sometimes an "allergenically denatured diet" is tolerated. In essence, this consists exclusively of thoroughly cooked foods, eliminating all raw or lightly cooked foods. Ascorbic acid should be administered to compensate for the loss of vitamin C in cooking.

a) HYPOSENSITIZATION

This is achieved by means of administration of slowly increasing quantities of the identified food allergen. The method is feasible in principle, in practice, however, it takes too long, and is not always without danger. Thus Sales, Debray, and Verdier reported allergy to milk in twins, with vomiting, diarrhea, and constitutional symptoms. One child was successfully hyposensitized, while the other infant, treated in the same manner, died of anaphylactic shock. Cathala, Ducas, and Netter²¹⁰ described another case in which hyposensitization was unsuccessful. 5 drops of milk elicited severe general manifestations.

b) SKEPTOPHYLACTIC DEALLERGIZATION

Three quarters of an hour before the meal, small doses of all the foods that will be served are administered orally, beginning with 0.1 to 0.2 Gm., and increasing to 5 or 10 Gm. within four weeks. This method is certainly irksome in practice, and it takes several weeks before the desired results can be achieved.

Skeptophylactic deallergization by means of

specific food propeptans is discussed on page 217.

2. METASPECIFIC THERAPY

Umber claimed to have cured cases of allergic diarrhea by means of subcutaneous injections of peptone. Kalk induced anaphylactic shock with horse serum in intractable cases of mucous colitis. These measures are based on the concept of metaspecific hypersensitization. However, the second method mentioned is a rather heroic one.

3. SYMPTOMATIC THERAPY

Epinephrine brings at least temporary relief in acute attacks. Atropine, syntropan, or other synthetic atropine-like drugs may be given by mouth to reduce the incidence of recurrences. Sedatives are useful both during the acute episode and for a few days thereafter. Dorst and Morris^{1579 1680} and Burger¹⁶⁸¹ believe that sodium ricinoleate (soricin) has a detoxifying effect on pathologic intestinal flora. Colonic irrigations are often beneficial in allergic disease of the intestines.

CHAPTER XXIV

ALLERGIC DISEASES OF THE LIVER AND GALLBLADDER

A LIVER

THERE are two possible relationships between hepatopathy and allergic diseases. In the first place, a primary liver disease—or at least impairment of hepatic function—may be the predisposing and sometimes even the causative factor in an allergic state. Conversely, the liver damage may result from an antigen-antibody reaction. Which of these two mechanisms is operative in a case evidencing hepatic involvement must be determined in each instance.

1. PATHIOGENESIS

Experimental studies provide adequate proof of the rôle of the liver in anaphylactic shock in dogs, as explained more fully on page 84. There is also some evidence that disturbed liver function plays an important part in certain cases of human allergy. Paul and Végh²⁴⁸ demonstrated hepatocellular damage in some allergic patients by showing that the blood chloride level following administration of sodium chloride by mouth is altered in the same way as in cases of liver disease. These authors assume that this is due to water retention in the diseased liver parenchyma. According to Galup, the proteopexic function of the liver is often disturbed in allergic conditions, as indicated by the so-called hemoclastic crisis of Widal. Barber and Oriol²⁴⁹ and Cameron²⁴⁵ found an increase of blood amino acids in a large number of paroxysmal manifestations of allergic nature and interpreted this finding as evidence of impaired liver function. Shay and his associates²⁴⁵ frequently observed positive brom sulfalein tests in such cases.

Allergic damage to the liver and the development of allergic hepatopathy are believed to take place in the following manner (Fornet). Even under perfectly normal nutritional conditions some foreign protein makes its way through the intestinal wall and eventually

arrives, unaltered, in the portal vein (Yoshiyuki²⁴⁶). However, this protein is retained and so broken down by the liver that it loses its antigenicity (Dujardin and De camps²⁴¹). But this function is limited on the one hand by the quantity of protein involved, and on the other by the individual capacity of the human or animal liver. In cases in which, as a result of disease or changes in the gastro intestinal mucosa, large quantities of inadequately digested substances, acting as antigens, come into the portal circulation, they first reach and may thus allergize the liver. When the same antigen again enters this organ, the resulting antigen-antibody reaction brings about parenchymal damage, manifested clinically by catarrhal jaundice. If this assumption could be confirmed experimentally, one might well be entitled to consider some instances of catarrhal jaundice and even of cirrhosis as being of allergic origin.

In this connection, the experimental investigations of Hartley and Lushbaugh²⁵⁰ are of particular interest. Rabbits sensitized with crystalline egg albumin showed large areas of coagulation necrosis of the liver parenchyma after injection of the antigen into the peritoneal cavity or the mesenteric veins. The authors concluded that focal necrosis of the liver was a direct result of the local union of the antigen and antibody.

For the purpose of demonstrating allergic hepatic damage, appropriate liver function tests should be performed both during and after allergic attacks.

2. SYMPTOMATOLOGY

Liver disease of allergic origin is characterized, at least in the early stages, by the sudden appearance of symptoms at irregular intervals. The liver is enlarged and painful. There are also headaches, and the skin temporarily presents a subicteric color. Such sudden attacks of hepatic enlargement have

²⁴² PAUL B. and VÉGH P. *Klin. Wchnschr.* 14: 503, 1935.

²⁴⁸ CAMERON A. J. D. *N. J. & Rec.* 130: 525, 19.9.

²⁵⁰ HARTLEY G. J., and LUSHBAUGH C. C. *Am. J. Path.* 15: 323, 1942.

been described by Glénard and Vinchon,²⁵⁵ among others, and are sometimes accompanied by various phenomena of allergic nature (urticaria, attacks of sneezing), and occasionally even by shocklike manifestations (G. Singer). Hepatic conditions of this kind have been observed in cases of hypersensitivity to food (veal, R. Gutmann^{255a}), and to tetanus antitoxin (Flandin and Vallery-Radot²⁵¹) and Witte peptone given by injection (Urbach).

3. THERAPY

Aside from elimination of the allergen (food or drug), the patient must be put on a strict liver-sparing diet. This should be rich in carbohydrates, vegetables, and vitamins, and poor in fats, salt, and spices; alcohol must of course be entirely forbidden. In order to increase storage of glycogen in the liver cells, it is advisable to administer large quantities of dextrose two or three times daily, and simultaneously to inject 5 to 10 units of insulin. Lastly, stimulation of the liver cells by intravenous decholin therapy is advisable (Shay and associates²⁴⁸).

B. GALLBLADDER

Flandin and Vallery-Radot²⁵¹ and Parturier²⁵⁶ were the first to express the view that certain cases of biliary colic are due to allergy to some food. They based this concept on analogy to similar manifestations following repeated horse serum injections, autohemotherapy, and sanguineous extravasations, as well as sunburn in individuals hypersensitive to sunlight. It was pointed out long ago—particularly in the French literature—that biliary colic is rather frequently associated with migraine. Kelling²⁵⁷ goes so far as to regard many such attacks as equivalents of migraine, and uses the term abdominal migraine in this connection.

1. PATHOGENESIS

On the basis of extensive investigations, Fodor and Kunos claim that the histories of one-fourth of all their cholecystopathy patients included mention of some previous allergic

condition, while the corresponding figure for other diseases investigated was only 5 per cent. Eiselsberg²⁵⁸ called attention to the nutritive-allergic origin of many cases of gallbladder colic, and advanced proof of the allergic pathogenesis by showing that the spasm failed to appear after ingestion of the food allergen when this was preceded by administration of the specific propeptan, and that it reappeared when the food in question was taken without the propeptan. Black²⁵³ and Pascual and Ramos, among others, reported similar cases of nutritive allergic origin, controlled by elimination of the allergenic food from the diet.

However, hypersensitiveness of the gallbladder need not necessarily relate to food, drugs, as well as injections of animal serum and of liver (Adelsberger and Munter¹⁰⁹), may also lead to allergic biliary colic.

In animal experiments, Fischer and Kaiserling²⁵³ succeeded in producing allergic cholecystitis by injecting sterile antigens into the efferent lymph vessels of the gallbladders of sensitized animals. Furthermore, Deissler and Higgins²⁵⁹ as well as Kallós and Kallós-Defner,¹³ showed that contact with the allergen caused contractions of the isolated gallbladders of sensitized guinea pigs. Passive sensitization of the gallbladder of the monkey was achieved by Walzer et al.²⁶⁰ by means of injections of a human serum containing antibodies for cottonseed protein. Within one to two minutes after injection of cottonseed extract into the popliteal vein one week later, an allergic reaction developed characterized by edema, hyperemia, and increased secretion of mucus, and histologically by a cellular infiltrate rich in eosinophils. Macroscopically, the reaction closely resembled that induced in the mucous membranes of the ileum, colon, and rectum in human beings.

In addition, absorption of undigested protein through the mucous membrane of the gallbladder, as well as of the common duct, was shown in ingenious experiments by Harten and his associates.²⁶¹

The great importance—both to the patient

²⁵⁵ EISELSBERG, K. P. *Klin. Wchschr.* 12: 1174, 1933.

²⁵⁹ DEISSLER, K., and HIGGINS, G. M. *Proc. Staff Meet., Mayo Clin.* 9: 678, 1934.

²⁶⁰ WALZER, M., GRAY, I., HARTEN, M., LIVINGSTON, S., and GRAYNE, D. *Gastroenterol.* 1: 363, 1943.

²⁵⁵ GLÉNARD, R., and VINCHON, J. *Presse méd.* 37: 403, 1929.

²⁵⁶ PARTURIER, G. *ibid.* 32: 819, 1924.

²⁵⁷ KELLING, G. *Arch. f. Verdauungskr.* 30: 59, 1922.

and to the physician—of knowing that gall bladder conditions of this kind are occasionally due to allergy is perhaps best brought out by the fact that totally unnecessary and completely futile operations have not infrequently been performed in such cases. Thus Rowe⁷¹⁰ Alvarez⁷¹¹ Graham and his associates⁷⁵⁹ Eiselsberg⁷⁵⁸ and others reported cases that were operated on and even drained on the basis of a diagnosis of chronic cholecystitis and in which the attacks persisted nevertheless until the true causes were discovered. These included hypersensitivities to egg, ham and fish (Eiselsberg) and to wheat (Graham) and correct diagnosis led to proper therapeutic measures such as

2. SYMPTOMATOLOGY

A hitherto healthy individual who does not have any digestive complaints, constipation or diarrhea may suddenly suffer cramplike pain in the right upper quadrant of the abdomen frequently radiating to the back and right shoulder and thus precisely simulating the picture of cholelithiasis. The region of the liver and gallbladder will be found to be markedly tender on palpation as may also to a less marked extent the small and large intestines. A cholecystogram may reveal no gallstones but rather a hydrops (Figs. 304, 305). Later there is belching, vomiting (after which the pains not infrequently cease



FIG. 304. CHOLECYSTOGRAM SHOWING HYDROPS DUE TO HYPERSENSITIVENESS TO LOBSTER.



FIG. 305. SAME PATIENT IN SYMPTOM-FREE STATE. GALLBLADDER NORMAL IN SIZE AND SHAPE.

elimination of the allergenic foods from the diet or administration of specific propeptans. Bauer⁷⁴⁰ reported a patient who had been suffering from severe pain in the right side of the epigastrium and migraine—symptoms strongly suggesting cholecystitis. Laparotomy revealed occlusion of the sphincter of Oddi by acute edema, probably of allergic nature.

Lastly, the discovery of an underlying allergy in these cases is of great importance inasmuch as repeated biliary colic may cause disturbances in the formation of bile and so lead sooner or later to production of gallstones.

abruptly) diarrhea, sometimes migraine and occasionally even urticaria. These attacks are never accompanied by fever; however, there are often vertigo, tremor, a feeling of weakness, palpitation and sometimes loss of consciousness. The acute episode can usually be controlled by an injection of epinephrine and this fact is an important diagnostic aid. Examining the patient on the following day, the physician is likely to be struck by the complete absence of tenderness over the gall bladder region.

Determination of the fact that a given case of cholecystopathy is of allergic origin will enable the physician to understand why the patient can tolerate foods that are generally

⁷⁵⁹ ALVAREZ, W. C. Proc. Staff Meet. Mayo Clin. 9: 680, 1934.

⁷⁶⁰ GRAHAM, E. A., COLE, W. H., COVER, G. H. and MOORE, S. Diseases of the Gall Bladder and Bile Ducts. Philadelphia: Lea, 1928.

undesirable in gallbladder conditions (e g , fat, mayonnaise), whereas attacks are evoked by ingestion of apparently innocuous foods such as white bread or lean beef.

According to Cancado,²⁵² with increasing experience the diagnosis of allergic cholecystopathy is being made more frequently. The absence of typical or characteristic symptoms and signs of an organic lesion, and the presence of a personal or family history of allergy support the diagnosis. Skin tests and eosinophile studies are of limited value.

3. THERAPY

In addition to the measures recommended for the treatment of allergic diseases of the liver, it is advisable in severe cases to remove the affected gallbladder surgically. Before resorting to operation, however, elimination diets, biliary drainage and decholin therapy should be given an adequate trial.

Not infrequently allergic cholecystopathy is accompanied by similar hepatic involvement. Such cases may be managed by a combination of the therapeutic approaches for the two conditions.

²⁵² CANCELO, J. R. *Rev. med.-cir. do Brasil* 52: 157, 1944.

ALLERGIC SKIN DISEASES

A THE SKIN AS AN ORGAN
OF IMMUNITY

WHY is the skin so frequently the site of allergic manifestations? And why do the latter assume so many different forms? These questions have been asked many times. In contrast to the skin in this respect the mucosa regularly reacts with uniform symptoms. Thus with regard to their manifestations it is impossible to differentiate between a case of hay fever and a rhinopathy due to dust or to a mold and an asthma based on allergy to some food presents the same symptoms as does infectious asthma.

The answer to the first question—as to the high incidence of allergic skin diseases—is that as will be shown below the skin produces antibodies much more rapidly and in greater quantity than does any other tissue. And the clinical variety of the responses can be explained at least in part by the fact that when the epidermis is the shock tissue (i.e. contains the specific antibodies) the reaction takes the form of an acute epidermitis while neurodermatitis on the other hand is based on hypersensitiveness of the cutis and urticaria on hypersensitiveness of the blood vessels of the skin.

The presence of antibodies in the skin explains the usefulness of the cutaneous tissues for scratch and intracutaneous tests for hypersensitivities in other organs. Moreover the antigen-antibody reaction that takes place after the introduction of the antigen into the antibody-containing skin can also be used for therapeutic purposes—not only in allergic dermatoses but also in all manner of other allergic diseases provided the antibodies in the cutis and in the shock tissues are the same. For all these reasons a brief discussion of the skin as an organ of immunity appears to be in order. (For details and bibliography the reader is referred to Tuft²⁹⁴ W. Jadassohn^{295a} and Urbach⁴¹⁶).

A distinction must be made between non-specific and specific reactivity of the skin. The former is a phylogenetic inherent property of the integument—i.e. having been exposed to all kinds of damage the skin has apparently learned to mobilize appropriate defenses to cope with a wide range of situations. The specific reactivity of the skin on the other hand may well be the result in the majority of cases of a previously acquired specific sensitization.

For centuries man has instinctively known how to make therapeutic use of the nonspecific reactivity of the cutaneous organ. Sun water and air baths, skin massage and all kinds of counterirritation were prescribed in ancient times and were as important then as are now such measures as ultraviolet irradiation, iontophoresis with histamine or choline and hydrotherapy.

It has long been known that a strong cutaneous response exerts an influence on the entire organism in the exanthematous infections. Clinical observations have to a certain extent supported the old popular belief that in variola, measles, scarlet fever and typhoid the more severe the skin eruption the less the internal organs suffer. Along the same lines are the common observations that a syphilitic who has severe skin lesions in the secondary stage is far less likely to develop visceral or nervous involvement and conversely that an arsenphenamine dermatitis indicates a favorable prognosis as regards syphilis and that patients with tuberculosis of the skin hardly ever have severe involvement of the lungs. The generally accepted explanation of these phenomena is that as a result of the particularly intense specific stimulation of the skin there are formed in this tissue sufficient antibodies to protect the entire organism. E. Hoffmann calls this function of the skin *esophylaxis* in contradistinction to *exophylaxis*, a term he applies to the purely mechanical protective function.

In addition to these important but merely clinical observations attempts have been

²⁹⁴ Tuft J. J. Immunol. 21: 85, 1931.

^{295a} J. DASSOW, W. Die Immunologie d. Haut. Handb. d. Haut u. Geschlechtskr. 2: 33, 193.

made during the past few years to determine experimentally the rôle of the skin in the immunity of the organism as a whole. Since these immunologic processes are characterized by the production of specific antibodies, attempts have been made to demonstrate their presence by means of passive transfer tests. Taking as his point of departure J. Jadassohn's report of a case in which hypersensitiveness to iodoform could be called forth only in a skin site covered with epithelium and not in a de-epithelialized area, Bloch⁵⁵⁶ attempted, by means of Thiersch skin grafts, to transfer iodoform hypersensitiveness to a previously insensitive subject. The success of this experiment led him to conclude that the presence of specific cellular antibodies in the epidermis of the patient had been demonstrated. Significant as these transplantation experiments may be in principle, they are not conclusive, for transplantation from man to man is possible only under certain special pathologic conditions (e.g., the reticulo-endothelial system must be blocked). Nevertheless, Bloch's concept that allergic dermatitis depends on the presence of epidermal antibodies was correct, and was later proved by Naegeli's autotransplantation method⁶⁶⁹ (p. 154).

Other lines of investigation have proceeded from Fellner's experimental work.⁶⁶³ He succeeded in showing that tissue obtained by curettage of a papular tuberculin reaction possesses specific enhancing properties: for addition of substances derived from the papule content to a dilution of tuberculin that ordinarily would produce no response will elicit a strongly positive skin reaction when applied to a scarified skin site. Not only was Fellner able to make weak tuberculin concentrations effective by addition of these substances, but he also, in 5 instances, achieved passive transfer of local tuberculin hypersensitiveness to previously anergic individuals. These skin-reaction-enhancing substances in the tuberculin papule were termed "procutines" by Fellner, and regarded by him as antibody-like in nature. Fellner's findings were confirmed and amplified by Martenstein and Schapiro.⁵⁵⁷

Moreover, by means of a special experimental method (i.e., excision of the injection site shortly after inoculation), Martenstein demonstrated that the antibodies are first produced in the skin, including the unaffected portions, and are only subsequently present in the serum.

As Trost has shown, tuberculous procutines are also found in the content of the blisters sometimes resulting from intradermal injection of tuberculin in highly sensitive patients. Procutines were also demonstrated in the serum of blisters artificially induced over the skin lesions of lupus erythematosus and erythema nodosum, whereas no procutines could be found in blisters similarly produced over the affected skin in dermatitis, urticaria, or psoriasis (Leiner).

The fact that cellular antibodies are formed in the skin of patients with allergic dermatitis, and that these antibodies do not enter the blood stream, or do so only in small amounts, was proved by the senior author⁵⁵³ following the suggestion of Koenigstein. This conclusion was based on the passive transfer of epidermal hypersensitiveness by means of blisters arising spontaneously or induced artificially by means of cantharides plaster on the allergized skin. To date, it has been possible by this method to demonstrate the presence of cellular (fixed histiogenic) antibodies in about 36 cases, as reported by a number of authors (p. 153). We should like to emphasize here that, contrary to some statements in the literature, the Urbach-Koenigstein method is not merely a modification of the Prausnitz-Kuestner procedure: the former elicits a delayed tuberculin type reaction, while the response in the latter is of the immediate type.

The conclusion reached on the basis of passive transfer experiments, that the skin is the site of formation of specific antibodies in various allergic conditions, is further supported by the fact that, in man, intracutaneous injections of foreign serum produce a greater degree of cutaneous hypersensitiveness than do the same doses injected intravenously (Koehler and Heilmann⁵⁷³). According to Haxthausen,⁵⁵⁸ the difference is particularly striking when small quantities of antigen are used. This is interpreted as indicating that a

⁵⁵⁶ BLOCH, B.: *Paris méd.* 33: 251, 1923

⁵⁵⁷ MARTENSTEIN, H., and SCHAPIRO, B.: *Deutsche med. Wchschr.* 49: 947, 1923

⁵⁵⁸ HAXTHAUSEN, H.: *Acta dermat.-venereol.* 20: 396, 1939.

large part of the effective cutaneous antibodies are actually formed in the skin itself. Furthermore, Grove²⁵⁹ and Kahn¹⁵³ have shown that while the titer of humoral antibodies in experimental animals is decidedly lower when the injection is given subcutaneously or intracutaneously than when it is made intravenously, the local hypersensitivity is greater in the first instances. Finally that the skin is a primary and independent producer of antibodies is indicated by the facts that simple chemical substances when mixed with foreign serum, sensitize on application on or into the skin, that the allergic reaction thus elicited is confined to the skin, and that such procedures do not, as a rule, evoke demonstrable antibodies in the blood serum (Haxthausen^{259b}).

That the skin also participates in the formation of antibacterial immune bodies was shown by Fernbach and Haessler²⁶⁰. Tuft and his associates²⁶¹ demonstrated that the intracutaneous route, with a one tenth dose of typhoid vaccine, produced a stronger and more lasting response than did all other routes with the exception of the intravenous, and even the latter route was less satisfactory in that the antibody titer was found to decline more rapidly. Matsumoto²⁶² observed that infinitely better immunologic results were achieved with bacterial vaccines when they were introduced directly into the skin than when they administered subcutaneously or intravenously, the best results were obtained when the vaccine was injected into a cantharides blister. Similarly, Hansel²⁶³ and others report better results with intracutaneous administration of pollen extracts in hay fever, particularly for coseasonal treatment when a rapid rise in antibody titer is urgent. The present writers, on the same grounds, prefer the intradermal route for hypsensitization to dust.

Percutaneous experiments corroborate the importance of the skin in the formation of antibodies. Repeated application of staphylococcus toxoid to the skin produces not only a

local immunization of the treated skin site but also a general immunity. In a series of experiments Mondolfo²⁶³ demonstrated that the skin areas that had been in direct contact with the toxoid contained a far greater antibody supply than did areas not previously so treated, thus it was observed that the former sites responded with only trifling local manifestations to injections of toxin while the latter gave necrotic reactions. Tonkato and Ozu²⁶⁴ demonstrated experimentally (by excision of skin sites previously rubbed with immune salves) that more than 70 per cent of the antibodies found in the blood had been produced by the prepared skin area, whereas only some 30 per cent had been supplied by the other organs.

The question also arises as to which part of the skin—the epithelium or the corium—is capable of producing antibodies. Clinical observations and the results of experimental investigation would seem to indicate that antibody production is dependent upon the cells of the reticulo endothelial system. This system is represented by the Langerhans cells in the epidermis and cutis and by the endothelium of the papillary blood and lymph capillaries. This serves to explain the fact that both the epidermis and the cutis are in principle, capable of producing antibodies.

The presence of specific antibodies in the skin in certain allergic diseases, as proved by the experimental investigations discussed above, has, aside from its purely theoretic interest, a far reaching practical importance. For both cutaneous allergy and cutaneous immunity are dependent upon specific epidermal and cutaneous antibodies this permits us to understand the biologic mechanism and diagnostic significance of skin reactions. Moreover, the presence of antibodies in the skin explains the results in certain infectious diseases, of those therapeutic methods that employ attenuated virus as the antigen provided it is introduced only into the epidermis (Jenner). This therapeutic approach also includes such procedures as the introduction of various antigenic substances (e.g., tuberculin) by application or inoculation (percutaneous

²⁵⁹ GROVE E. F. *J Immunol* 23: 101 1932

²⁶⁰ FERNBACH H. and HAESSLER E. *Zentralbl f Bakt* 75: 61 1925

²⁶¹ TUFT L. YAGLE E. M. and ROGERS S. *J Infect Dis* 50: 98 1932

²⁶² MATSUMOTO S. *Acta dermat* 28: 79 1936

²⁶³ MONDOLFO U. *Gior di batteriol e immunol* 22: 163 1939

²⁶⁴ TONKATO R. and OZU S. *Ztschr f Immun laetsforsch u exper Therap* 76: 413 1939

method of Petruschky and Moro), scarification followed by inunction (cutaneous method of Ponndorf), and the intracutaneous method (Wolff-Eisner). The last-named route has recently been highly recommended by Tuft,²⁶⁰⁵ Kern,²⁶⁰⁶ and others. The use of percutaneous hyposensitization in allergic contact dermatitis is discussed in greater detail on page 205.

While the skin assumes the largest share in the defense of the body by producing specific antibodies, the importance of certain mucous membranes should not be overlooked—particularly those coming into intimate and direct contact with bacteria and other antigens, such as the nasal and intestinal mucosa. Despite the fact that these linings lack the protection of the horny layer that provides the skin with an effective barrier, they nevertheless prevent bacterial invasion. The observations below, among others, strongly suggest that this immunobiologic defense is mediated by the formation of cellular antibodies. In this connection it is of more than historical interest that the Chinese, long before the time of Jenner, used the nasal route for vaccinating against smallpox, by inoculating cowpox lymph into the mucosa (Blumenfeld). In animal experiments, Bussacca succeeded in immunizing rabbits against *Bacillus paratyphosus* B, pneumococci, and smallpox by way of the nasal mucosa. Similar attempts employing the membranes of the mouth and trachea were unsuccessful. More recently, topical nasal application has been used for active immunization against tetanus (Gold¹⁷⁰⁶), diphtheria (Fraser et al.,²⁶⁰⁷ Dow²⁶⁰⁸), and bacterial infection (Walsh¹⁷⁰⁴). The serum antibody titer was definitely increased in cases so treated.

Experiments carried out particularly by Besredka¹¹⁵ have shown that the intestines likewise possess a particular ability to resist invading bacteria. While the French investigator claimed that this mechanism does not depend on the intervention of cellular

antibodies, the present authors are of the opposite opinion (see p. 23).

B. DERMATITIS (ECZEMA)

1. CLASSIFICATION

No other word in medical nomenclature is as loosely and as indiscriminately used as "eczema." The term has long been—and still is—a veritable wastebasket for various undiagnosed forms of inflammatory skin lesions. For this reason, the view is now widely held that it might be best to dispense with the word eczema entirely, and to replace it with terms based on etiology. At present, however, we are still obliged—despite remarkable progress in the last few years—to resort to some extent to morphologic criteria. Although "eczema" is a syndrome characterized by certain definite clinical and histologic characteristics, it has its origin in the most diversified external and internal conditions. Unfortunately it is impossible to differentiate between eczemas and dermatitides by the simple expedient of considering the former to be due to internal and the latter to external causes. Furthermore, it must be especially emphasized that every dermatitis is by no means of allergic nature. On the contrary, many a case is a reaction to an exogenous toxic agent, while others are due to diseases of the gastro-intestinal tract, endocrine dysfunctions, metabolic disorders, and so on. Infections and parasitic agents also play an important part.

It would take us too far afield to undertake anything like an exhaustive discussion of the numerous attempts that have been made to classify "eczemas" into categories. The most significant efforts in this direction have been contributed by Sulzberger,⁴ Stokes,⁶ Bonnevie,²⁶⁰⁹ Burckhardt,²⁶¹⁰ Robinson,²⁶¹¹ and Epstein.²⁶¹²

We propose to distinguish between eight principal groups:

Contact Dermatitis (syn. epidermatitis, epidermitis)

²⁶⁰⁵ TUFT, L. *J. Lab. & Clin. Med.* 16: 352, 1931

²⁶⁰⁶ KERN, R. A., CRUMP, J., ROOD, R. L., and BOROW, S. *J. Allergy* 9: 125, 1938

²⁶⁰⁷ FRASER, D. T., DAVEN, E. L., and HALPERN, K. C. *Canad. Pub. Health J.* 31: 376, 1940

²⁶⁰⁸ DOW, R. P. *ibid.* 31: 570, 1940

²⁶⁰⁹ BONNEVIE, P. *Ätiologie und Pathogenese der Ekzemkrankheiten*. Leipzig: Barth, 1939

²⁶¹⁰ BURCKHARDT, W. *Dermatologica* 81: 196, 1940

²⁶¹¹ ROBINSON, H. M. *Clinics* 3: 834, 1944

²⁶¹² EPSTEIN, S. *Ann. Allergy* 2: 217, 1944

Allergic Dermatitis From Within

- a due to food
- b due to drugs

Neurodermatitis

Infantile Dermatitis

Seborrheic Dermatitis

Infectious and Parasitic Dermatitis

Metabolic Dermatitis

Dermatid

While this division is based primarily on pathogenetic grounds, we are nevertheless obliged to make at least some use of clinical criteria, as, for example, in the instances of infantile dermatitis, neurodermatitis, and seborrheic dermatitis.

Needless to say, these groups do not represent sharply defined entities. On the contrary, transitional forms are frequently encountered, so that it is often difficult to know, for example, whether one is dealing with an infantile dermatitis or with seborrheic dermatitis in an infant. Moreover, not very infrequently a single patient will present two types of "eczema" simultaneously—e.g., contact dermatitis and neurodermatitis. Despite all these difficulties, adequate classification is absolutely essential for therapy based on etiologic considerations.

2 CONTACT DERMATITIS (EPIDERMATITIS, EPIDERMITIS)

Contact dermatitis is the term that has come into general acceptance to designate the cutaneous manifestations caused by surface contact* with the excitant. However, some confusion has resulted from the use of this term. The expression is most commonly understood to refer to allergic contact dermatitis, even though the word allergic is often omitted. Yet there are numerous instances of nonallergic dermatitis produced by contact with chemicals and other substances. For therapeutic as well as prophylactic reasons, it is therefore necessary to indicate specifically, by means of a proper term, whether one is dealing in a given case with a nonallergic or with an allergic contact dermatitis.

For the sake of clarity, we prefer the divi-

sion of contact dermatitis into the toxic and the allergic types. The term toxic is employed not in the narrow pharmacologic meaning, but rather in a broader sense. According to the definition arrived at by the Consulting Staff of the Dermatoses Investigations Section of the United States Public Health Service in 1942²⁶³ a primary cutaneous irritant is an agent that will produce a clinically manifested irritation at the site of contact on the normal skin of a majority of persons not previously sensitized to that substance if it is permitted to act in a given concentration in a given vehicle and after a given manner and length of exposure. The irritation may be redness, papulation, vesiculation, ulceration, or other sign of damage at the site to which the irritant has been applied. Substances of this type are for example, certain inorganic and organic acids, alkalies, salts, solvents, oils, and dye intermediates that are capable, particularly after the skin has been traumatized by friction, light, heat, cold, or excessive perspiration, of exerting a nonspecific toxic (often caustic) action—in other words, there is usually a chemical and mechanical injury to the skin.

By contrast, a cutaneous sensitizer is an agent which is incapable of producing demonstrable cutaneous changes on first contact, except in persons hypersensitive to it, but which may increase the tissue capacity to react to subsequent exposure after a suitable latent period as manifested by dermatitis after further contact on the same or other parts of the body. A primary irritant may also be a sensitizer depending on the concentration of the chemical, the period of contact, and other conditions of exposure.

Other designations for contact dermatitis, in the broader sense are dermatitis venenata, industrial dermatitis, occupational dermatitis, and, as proposed by Downing²⁶⁴ "ergodermatosis" (Greek *εργον*, "work," and *δερμα*, "skin"). Epstein²⁶⁵ has recently advanced the term "epidermitis" and Templeton,¹⁵⁹ "epidermatitis," as indicating the shock tissue and the pathologic findings more precisely, and avoiding the ambiguity of thought in

*It is apparent that agents producing contact dermatitis either during clinical exposures or when applied as patch or other tests must first penetrate the natural barriers of the skin's surface and reach at least the living epidermal cells.

²⁶³ Dermatoses Investigation Section, U. S. Pub. Health Service, Arch. Dermat. & Syph. 43: 1167, 1942.

²⁶⁴ Downing, J. G. Arch. Dermat. & Syph. 39: 12, 1939.

herent in the word "contact," since the allergen need not always reach the epidermis from without. Table 57 presents a number of synonyms for the two subgroups of contact dermatitis, containing terms frequently found in the literature.

It cannot be denied, however, that it is often difficult to determine whether a given case is one of toxic or of allergic contact dermatitis. The clinical pictures, especially in the advanced stages, are identical. Moreover, Miescher²⁶¹⁹ has shown that while the histologic finding of spongiotic vesicles is characteristic of the allergic eczematous reaction, it is not, in itself, conclusive evidence; for this type of reaction is also elicited by agents of

was suggested by Schwartz²⁶²¹. He believes that this is achieved chemically by affecting the pH of the sweat, which in turn affects the ability or capacity of sweat both in its action as a solvent for and as a neutralizer of external irritants. He emphasized that if a worker is exposed to an alkaline irritant and has a markedly acid perspiration, the latter would tend to neutralize the chemical, while if his sweat is alkaline it would enhance the irritant action of the alkali. In this connection should be mentioned the observations of Zingsheim,²⁶²² who employed the method of Burckhardt²⁶²³. Zingsheim found that the capacity of the skin to neutralize alkali varied with certain dermatoses, in occupational and age groups, and

TABLE 57—Synonyms for the Two Types of Contact Dermatitis

Toxic Group	Allergic Group
Toxic contact dermatitis (Burckhardt ²⁶¹⁹)	Allergic contact dermatitis (Burckhardt ²⁶¹⁹)
Nonsensitization dermatitis (Downing ²⁶¹⁴)	Sensitization dermatitis (Downing ²⁶¹⁴)
Noneczematous industrial dermatitis (Foerster ²⁶¹⁶)	Eczematous industrial dermatitis (Foerster ²⁶¹⁶)
	Eczematous contact-type dermatitis (Sulzberger ⁴)
Unspecific contact eczema (Becker and Obermayer ²⁶¹⁷)	Specific contact eczema (Becker and Obermayer ²⁶¹⁷)
Eczematoid contact dermatitis (Netherton ²⁶¹¹)	Eczematous contact dermatitis (Netherton ²⁶¹¹)
Toxic epidermitis (Epstein ²⁶¹²)	Allergic epidermitis (Epstein ²⁶¹²)
	Allergic occupational dermatitis of contact type
	True eczema (German school)
	Dermatitis eczematosa
Traumatic contact dermatitis	

proved toxic nature. The principal difference is that in toxic contact dermatitis, patch tests with nontoxic concentrations of the causative substance (i.e., those incapable of causing reactions in normal individuals) are negative, while in the allergic form they are positive. Finally, it cannot be denied that toxic irritation of the skin often paves the way for a specific allergization.

Important constitutional conditions favoring the acquisition of contact dermatitis are oily skin, ichthyotic skin, and hyperidrosis (Stokes²⁶²⁰).

The possibility that a worker's diet has an influence on susceptibility to external irritants

with the degree of allergization. The neutralization time was found to be prolonged in laborers, bricklayers, masons, and the like.

Contact dermatitis is constantly assuming greater significance. Schwartz²⁶²⁴ showed that the annual incidence of occupational dermatoses in the United States, even before World War II, affected at least 1 per cent of all industrial workers, and more time is lost from work because of them than from any other occupational disease. Still more important, however, is the fact that the incidence is relatively much higher in certain industries. Thus, 20 per cent of all occupational dermatoses are encountered in metallurgical industry; next in order of frequency are those among domestic help and food industry workers.

²⁶¹⁹ Idem J A M A 115, 813, 1940

²⁶¹⁶ FOERSTER, H. R., Wisconsin M J 40: 377, 1941

²⁶¹⁷ BECKER, S. W., and OBERMAYER, M. E., Modern Dermatology and Syphilology Philadelphia Lippincott, 1940

²⁶¹¹ NETHERTON, E. W., Pennsylvania M J 48: 1025, 1945

²⁶¹² MIESCHER, G., Arch f Dermat u Syph 177: 8, 1938

²⁶²⁰ STOKES, J. H., J A M A 98: 1127, 1932

²⁶²¹ SCHWARTZ, L., J Indiana State M A 31: 379, 1938

²⁶²² ZINGSHEIM, M., Dermat Wchnschr 110: 238, 1940

²⁶²³ BURCKHARDT, W., Arch f Dermat u Syph 178: 1, 1938

²⁶²⁴ SCHWARTZ, L., J A M A 111: 1523, 1939

Foerster,²⁶⁷⁵ Lane,²⁶⁷⁶ and Hall²⁶⁷⁷ have pointed out that, exclusive of industrial accidents skin conditions represent approximately 65 per cent of all occupational diseases. Here again it is interesting to note that the majority of the cases are caused by some toxic agent. In a series of no less than 10 000 instances of occupational dermatosis Schwartz²⁶⁷⁸ found only 18 per cent to be of strictly allergic origin. However, this too varies with the industry. Thus, the allergic form of occupational dermatitis occurred more frequently in the manufacture of munitions than in other war plants (Schwartz²⁶⁷⁹). Klauder²⁶⁸⁰ analyzed 527 cases diagnosed as occupational dermatitis according to the actual causes. In only 12.5 per cent could a sensitization dermatitis be established, due to petroleum products anti corrosion oils, linseed oil, vanilla, cinnamon, insecticide glue, chemicals, permanent wave lotion, scalp lotions, rhus, ragweed, chrysanthemum, and colored paper. However, Klauder placed the large group of cases caused by turpentine and chromates in the primary irritant group without routinely studying them with the patch test method for contact allergy. Many authors believe that dermatitis from turpentine always connotes sensitization and previous exposure (Perutz).

The fact that the combination of toxic and allergic actions may be operative in industrial dermatitis is being increasingly recognized. However, it is often difficult to evaluate correctly in some cases to what extent the condition is caused by primary irritant properties of the chemical agent and how much is due to an allergic hypersensitiveness to it.

Compilations of the primary irritants and skin hazards involved in various occupations, and their prevention, are available from several sources, including Weber²⁶⁸¹ and Schwartz.²⁶⁸²

Physicians obliged to deal with industrial cases should be familiar with the compensation laws of their own states. The medicolegal

aspects of occupational dermatoses are thoroughly discussed by Foerster,⁶ Sulzberger and Finnerud,²⁶⁸³ Blaisdell,²⁶⁸⁴ Sappington,²⁶⁸⁵ and Schwartz.²⁶⁸⁷ Because of compensation claims it is important to determine whether a dermatitis is of industrial origin. The Committee on Occupational Dermatoses²⁶⁷⁸ set forth the following criteria for the diagnosis of occupational dermatoses:

a) An occupational dermatosis is one in which the rôle of an occupational causal (major or contributory) factor has at some previous time been established beyond reasonable doubt.

b) The person has been working in contact with an agent known to have produced similar changes in the skin.

c) The time relationship between exposure to the agent and the onset of the dermatosis is correct for that particular agent and that particular abnormality of the skin.

d) The site of the onset of the cutaneous disease and the site of maximum involvement are consistent with the site of maximum exposure.

e) The lesions present are consistent with those known to have followed the reputed exposure or trauma.

f) The person is employed in an occupation in which similar cases have previously occurred.

g) Some of the person's fellow workers using the same agent are known by the examiner to have similar manifestations due to the same cause.

h) So far as the examiner can ascertain there has been no exposure outside of occupation that can be implicated.

i) If the diagnosis is dermatitis the following items are important:

(1) Attacks after exposure to an agent followed by improvement and clearing after cessation of exposure constitute most convincing evidence of the occupational factor as a cause.

(2) The results of patch tests performed and interpreted by competent dermatologists corroborate the history and the examination in the majority of cases.

However, lapse of time between exposure and examination, impossibility of obtaining an accurate history, previous treatment, a combination of occupational and nonoccupational cutaneous disease and various other

²⁶⁷⁵ FOERSTER H R. *ibid* 107:247 1936.

²⁶⁷⁶ LANE C G. *ibid* 111:1521 1938.

²⁶⁷⁷ HALL E R. *J Tennessee M A* 34:22 1941.

²⁶⁷⁸ SCHWARTZ L. *J Allergy* 11:318 1940.

²⁶⁷⁹ *Idem* *Ann Allergy* 2:38 1944.

²⁶⁸⁰ KLAUDER J V. *Arch Dermat & Syph* 48:59 1943.

²⁶⁸¹ WEBER L F. *ibid* 35:123 1935.

²⁶⁸² SCHWARTZ L. *Occupational Diseases of the Skin*. Baltimore: Williams & Wilkins 1943. p. 296-314.

²⁶⁸³ FOERSTER H R. *J A M A* 111:1542 1938.

²⁶⁸⁴ SULZBERGER M B and FINNERUD C W. *J A M A* 111:1528 1938.

²⁶⁸⁵ BLAISDELL J H. *Arch Dermat & Syph* 39:69 1939.

²⁶⁸⁶ SAPPINGTON C O. *Medicological Phases of Occupational Diseases*. Chicago: Indust Health Bk Co 1939.

²⁶⁸⁷ SCHWARTZ L. *Ann Int Med* 18:500 1943.

²⁶⁸⁸ LANE C G, DENNIE C C, DOWNING J G, FOERSTER H, OLIVER E A and SCHULZBERGER M B. *J A M A* 119:613 1932.

factors prevent the application of any criteria in certain cases. It is also realized that all the suggested criteria will not fit every individual case. However, a careful weighing of the evidence obtained by detailed history and examination in the light of these standards, should aid in the interpretation of the occupational relationship.

by excretion of carbon dioxide the skin is able to neutralize to a certain extent the alkali with which it comes in contact. This process is delayed in individuals whose skins have become relatively less resistant to alkali. The same mechanism is probably involved in the majority of cases of dermatitis due to soap or other alkalis, which are the principal



FIG 306 TOXIC CONTACT DERMATITIS DUE TO WORKING WITH CEMENT

TOXIC CONTACT DERMATITIS

The majority of cases begin as erythema, at first sharply limited to the skin site touched by the irritant. Later the condition becomes papular, vesicular, and even pustular if secondarily infected. Quite commonly these lesions spread beyond the borders of the contact zone when the noxa is carried to other parts of the body—as, for example, to the genitaha.

Occupational primary irritants may be roughly divided into four groups:

The first type comprises keratolytics and other substances capable of cleaving or otherwise damaging the horny layer of the skin. This group consists chiefly of caustics and alkalis. The valuable work of Burckhardt²⁶²³ and of Sulzberger and Baer¹⁶³ has demonstrated that in patients with cement dermatitis ("mason's eczema") there is a decrease in the resistance of the skin to alkali (Fig 306). The lowering of the threshold of reaction was found to be directly proportional to the ability of the individual skin to neutralize alkali. In other words, exposure to cement produces dermatitis in persons whose skins neutralize alkali slowly. Burckhardt demonstrated that



FIG 307 TOXIC CONTACT DERMATITIS DUE TO LAUNDRY SOAP CARRIED TO FACE BY HANDS

causes of dermatoses in housewives (Fig 307), domestic servants, dishwashers, laundresses,

and even surgeons. This was largely confirmed by Theiler²⁶³ who found that of 74 cases of dermatitis in housewives 46 were due to the use of alkaline washing agents and waxes containing turpentine. 26 reacted on patch testing to alkalis and turpentine. 11 to alkalis alone. 9 to turpentine oil alone and the remainder to clothing, cosmetics, nickel, primrose and medicaments. While the hypersensitiveness to turpentine was allergic in character, the cases due to alkalis were shown to have an impaired alkali neutralization capacity of the skin by means of the Burckhardt test. As Klauder pointed out, the eczematogenous action of all alkaline cutaneous detergents may be explained by the concept that in these cases an alkaline substance becomes an irritant in a concentration to which the normal skin does not react. The mechanism underlying this form of hypersensitiveness is pathergic and should not be confused with allergic hypersensitiveness to soap. The latter is quite rare and when present is usually due to coloring matter, perfumes and other extraneous ingredients and only very occasionally to the alkali or fatty acids. On the other hand—as has been demonstrated by Burckhardt²⁷ in experimental animals and by Jordan and his associates²⁶⁰ in clinical experiments—the alkali in the soap by reason of its degreasing action paves the way for other agents to allergize the skin.

The second group of primary toxic irritants includes substances that are either fat solvents or are themselves soluble in fats, lipoids and oils.

The third group is made up of chemicals that can readily come into contact with the living cells, such as the dyes, paraphenylenediamine, dinitrochlorobenzol and amido azotoluene hydrochloride.

The fourth group is the most heterogeneous, it embraces primarily irritant chemicals such as explosives (tetra- and trinitrotoluene) and rubber accelerators (paranitrosomethylamine, mercaptobenzothiazole and tetramethylthiuram disulfide).

In view of the fact that the incidence of toxic contact dermatitis is constantly increas-

ing and that it very commonly causes at least temporary disability, the prophylaxis of this occupational disease is assuming increasing importance. Prevention of industrial dermatitis has received adequate attention only in the past few years. There are various approaches to this problem; the choice depending on whether the fault lies in the hygienic conditions of the plant or in the hygienic habits of the workers and on whether the substances encountered in the work are the causative agents or whether the methods employed to remove them from the skin are harmful.

The physician in charge should be in permanent consultation with the plant management and when necessary, with safety engineers and the plant chemist. The following preventive and protective technique is recommended by the leading authorities including Schwartz and Tulpan⁷¹⁷, Downing and Welch²⁶⁴, Klauder⁶⁴², Osborne and Jordan²⁶⁰, Foerster²⁶⁴ and Eller and Schwartz²⁶⁵. The prophylaxis should begin with selective employment. Before being accepted, new workers should be carefully examined for evidence of eczematous hypersensitiveness in general, but various skin infections including ringworm should also be given proper attention since such conditions may pave the way for allergization. In industries in which the materials handled are known to be highly allergenic—as in factories where synthetic dyes and complex organic compounds are manufactured—new applicants should be patch tested with the chemicals with which they will have to work and persons found to be hypersensitive should be rejected. Needless to say, this procedure does not guarantee that individuals failing to react will never acquire a skin disease, but the elimination of originally hypersensitive individuals will have been accomplished. However, the danger of sensitizing the applicant by means of the tests should not be overlooked. In place of the particular occupational chemicals, Sulzberger and Baer⁷²¹ recommend pre-employment patch testing with

²⁶³ THEILER E. *Dermatol. ca.* 84: 133, 1941.
²⁶⁴ DOWNING J. G. and WELCH C. E. *New England J. Med.* 206: 666, 1932.

²⁶⁵ KLAUDER J. V. *Indust. Med.* 9: 221, 1940.

²⁶⁶ OSBORNE E. D. and JORDAN J. W. *J. A. M. A.* 114: 1533, 1938.

²⁶⁷ FOERSTER H. R. *Rocky Mountain M. J.* 37: 410, 1940.

²⁶⁸ THEILER E. *Dermatol. ca.* 84: 133, 1941.

²⁶⁹ JORDAN J. W., DOLCE F. and OSBORNE E. D. *J. A. M. A.* 115: 1001, 1940.

the commonly encountered eczematogenic allergens (see list on p. 704).

Maintenance of the workers in a state of physical and mental well-being, attention to the hygienic conditions of the place of employment, introduction of safety devices, and mechanization of manual procedures, wherever possible, are all of primary value. The personal hygiene of the worker comprises cleanliness, including a shower after work, and suitable applications to the skin: these should be obligatory. Work clothing should not be worn on the street or for everyday purposes. Frequent changes of work clothes should be provided by the management, especially where oils are used in industrial processes. All employees should be periodically inspected and those showing evidence of irritation should be immediately excluded from their particular work. Substances with high eczematogenous indices should be eliminated or replaced, if possible. Processes involving the use of injurious chemicals should be completely enclosed. Where the irritant is a dust, fine powder, smoke, fume, or vapor, adequate local or general exhaust ventilation should be provided. The worker should be protected against irritating substances by wearing suitable protective clothing, such as fabric-lined rubber gloves, protective sleeves, aprons, masks, and goggles, and by the application of protective creams or liquids (described below). Soaps containing abrasives, excessive coconut oil, and free alkali are to be avoided.

A particularly important point is the prevention of dermatitis due to prolonged exposure to an alkaline cleanser (including soap). This may be achieved by the use of sulfonated oils, preferably vegetable oils, or "wetting agents." They emulsify the dirt and grease on the skin, and, being water-miscible, can be used as skin cleansers. Moreover, they have the additional advantage of not defatting the skin. Schwartz²⁶³ recommends a mixture of sulfonated castor oil with 2 per cent of fatty alcohol sulfates. Klauder and his associates²⁶⁴ recommend various combinations of sulfonated olive oil, light liquid petrolatum, sulfonated neat's foot oil, and aqueous solution of

gelatin, with or without added alcohol sulfate. Alkyl sulfonates are thought by some to produce dermatitis less often than the sulfonated oils, and Sulzberger suggests:

	Percentage
Cetyl alcohol	10-20
Sodium lauryl sulfate	1
Glycerin	10
Water	64-74

Readily available soap substitutes include Acidolate Skin Cleanser (National Oil Products Co., Harrison, N. J.), consisting of sulfated vegetable oils with water and mineral oil, and Lowila Cake (Westwood Pharmacal Corp., Buffalo 2, N. Y.), containing 5 per cent lauryl sulfoacetate diluted in bentonite. Another synthetic detergent, pHIsoderm (Fairchild Bros and Foster, New York 13, N. Y.) is a cream composed of a sulfonated ether, petrolatum, lactic acid, and wool fat cholesterol. Workers who are soap- or alkali sensitive, or who already have chronic dermatitis or dry fissured skins from the use of ordinary industrial cleansers, should use skin cleansing agents other than soaps.

The importance of cleansing agents in the causation of occupational dermatitis has only recently received adequate attention (Lane and Blank,²⁶⁵ Schwartz,²⁶³ Klauder and his associates²⁶⁴). It has been shown that a great number of cases of industrial dermatitis are caused annually not by the substances encountered in the work itself, but by removal of these chemicals by methods harmful to the skin (Overton²⁶⁶). Improper cleansing agents, as well as improper use of substances that are in themselves harmless, are responsible for more cases than is the occupational exposure itself (Horner²⁶⁷). A formula for a suitable industrial skin cleanser, according to Schwartz,²⁶³ is:

	Gm.
Neutral toilet soap	30
Colloidal clay (bentonite or kieselguhr)	30
Santomerse or other synthetic detergent	10
Lanolin	5
Perfume	1

Mix the colloidal clay and Santomerse. Heat the soap and lanolin and mix with these. This may be pressed into cake form, or 25 parts of corn meal may

²⁶³ SCHWARTZ, L. Pub. Health Rep. 56, 1788, 1941.

²⁶⁴ KLAUDER, J. V., CROSS, E. R., and BROWN, H. Arch. Dermat. & Syph. 41: 331, 1940.

²⁶⁵ LANE, C. G., and BLANK, I. H. J. A. M. A. 118: 804, 1942.

²⁶⁶ SCHWARTZ, L. M. Chin. North America 26: 1195, 1940.

²⁶⁷ OVERTON, S. Brit. J. Dermat. 41: 250, 1929.

²⁶⁸ HORNER, S. G. Lancet 2, 233, 1934.

be added to make up 100 parts, and the mixture then made into a powdered soap.

Another method for the prevention of occupational dermatitis was suggested by Prosser White,¹²⁸³ in the control or neutralization of chemical irritants wherever practicable. Thus, alkaline liquids may be neutralized by acetic acid (vinegar), citric acid (lemon juice), or weak sulfuric acid, followed by thorough rinsing in distilled water. For acid or oxidizing substances, a weak alkali or reducer is indicated. More recently, Anderson²⁶⁵¹ again stressed the approach that chemical antidotes to the primary skin toxin should be sought. They act by (a) neutralization or (b) detoxification by forming an insoluble or innocuous compound. Examples of the former have already been given. An example of the latter would be the oxidation of chromium compounds into innocuous metallic salts by sodium sulfite. In still another procedure, the phenomenon of adsorption might be utilized, using adsorbent powders such as charcoal and kaolin. Finally, the unusual emulsifying and detergent properties of the new wetting agents might be employed to remove toxic chemicals from the skin, both in prevention and perhaps even in therapy of the actual dermatitis.

Another practical approach is the use of protective preparations applied to the skin before work. They must be sufficiently adherent to the skin, incapable of sensitizing, and, according to the nature of the work, should be greasy, nongreasy, or waterproof, or particularly adapted for certain effects and purposes (formulas 1 to 7, below). A number of useful preparations based on similar principles are commercially available.

Formula 1 has a pH of 5.4 and is therefore recommended when there is prolonged contact of the hands with soapy water.

	Percentage
White wax (U S P)	10 0
Hydrous wool fat	5 0
Glyceryl monostearate*	12 5
Stearic acid	2 0
Petrolatum	70 5

* Anderson N P. *Indust Med* 12:584 1943. *Arch Dermat & Syph* 49:176 1944.

* Glyceryl monostearate may be obtained as Xerol A (Fries Bros.)

Formula 2 serves to waterproof the skin and is recommended when there is prolonged contact with water.

	Percentage
White wax (U S P)	10 0
Hydrous wool fat	5 0
Sulfonated olive oil	10 0
Petrolatum	75 0

Formulas 3 and 4 are clean nongreasy preparations that dry on the skin and do not rub off. Use of these is indicated, therefore, in dry work, as a protection against dust-borne irritants, and to avoid soiling of material or objects by the protective. Formula 3 is smeared on the skin, whereas formula 4 is liquid and applied by means of a brush or swab. Formula 3 is

	Percentage
Glyceryl monostearate	12 0
White wax (U S P)	12 0
Wool fat	6 0
Cholesterol	1 0
Sodium silicate commercial solution	5 0
Ammonium hydroxide 10 per cent solution	0 5
Water	63 5

Melt the white wax, glyceryl monostearate, hydrous wool fat, and cholesterol in one pot. Add the sodium silicate and ammonium hydroxide solutions to water previously heated in another pot. Stir the aqueous solution into the wax mixture.

Preparations of mastic solution in acetone will dry and leave a film on the skin. Formula 4 is

	Percentage
Ethyl cellulose	5 0
Mastic	8 0
Castor oil	1 0
Acetone	86 0

Use whole mastic, not powder. Allow the mastic to stand in the acetone overnight. A residue remains. Use the supernatant fluid as a solvent for the other ingredients. Apply the liquid by means of a brush or swab.

Formula 5 typifies a protective ointment containing nonirritant chemicals to neutralize industrial irritants. For instance, boric or benzoic acid are used to neutralize alkali, soaps and magnesium hydroxide to neutralize acids, and oxidizers such as dichloramine T or the various peroxides to detoxify vesicant gases.

	Percentage
Magnesium carbonate	5
Talc	5
Soap	30
Lanolin	30
Castor oil	28
Duponol	2
Perfume q s	

Mix soap, lanolin, and castor oil. Incorporate magnesium carbonate and Duponol

A protective ointment which permits inert powders to adhere to the skin, forming a protective covering against skin irritants is illustrated in Formula 6. The powders may be calamine, zinc oxide, iron oxide, kieselguhr, bentonite, and so on. This type is recommended for exposures to water-insoluble allergenic substances such as the chemicals used in the manufacture of explosives, and for protection against mechanical irritation due to abrasives, sharp pieces of glass, particles of steel, and thorns or fuzz on flowers, fruits, and vegetables:

	Percentage
Zinc oxide	5
Talc	5
Iron oxide	1
Irish moss	2
Gum benzoin	2
Water	10
Alcohol	15
Vanishing cream	60

Dissolve Irish moss in water. Dissolve benzoin in alcohol. Mix with powders and incorporate into vanishing cream.

A protective application against the photosensitizing action of heavy coal tar distillates and oil distillation residues, as well as excessive sunlight will be found in Formula 7. Such physical light screens as menthyl salicylate, esculetin, benzyl salicylate, quinine oleate, tannic acid, and tannates may be incorporated:

	Percentage
Lanolin	58
Castor oil	30
Titanium dioxide	5
Menthyl salicylate	5
Duponol	2
Perfume q s.	

Melt lanolin and mix with castor oil. Incorporate titanium dioxide, menthyl salicylate, and Duponol

Active treatment should begin with prompt and effective therapy of minor injuries, and

continued observation of them until healed. Once a dermatitis of some severity has developed, the patient should be removed from or at least protected against further contact with the causative agent, and appropriate dermatologic procedures should be instituted. If, on the other hand, the dermatitis is only beginning to appear, the hardening treatment of Schwartz and Tulipan⁷⁷ is to be recommended. According to this method, the patient continues to work while receiving local treatment. Very frequently the inflammation of the skin will disappear after a period of about two weeks. Where this does not occur, the worker must be removed from the job temporarily and, if trouble develops upon return to work, advised to follow a different occupation. It should be pointed out that in toxic contact dermatitis the mechanism in the majority of cases of "hardening" is not one of hyposensitization or deallergization, but merely of acquisition of nonspecific skin tolerance to chemical and physical irritation. On the other hand, in allergic contact dermatitis the observations of Peck, Gant, and Schwartz,⁷⁸ along with their review of the literature, seem to indicate that the process is a hyposensitization, or in our opinion one of deallergization. Koch⁷⁹ confirms the occurrence of a gradual regression of occupational dermatitis in some instances despite continuation of work, although the majority of his patients remained subject to dermatitis, and thinks that the only possible explanation is a hyposensitization, thereby presupposing specific allergic processes, although granting that various other factors may play a part.

ALLERGIC CONTACT DERMATITIS

While toxic contact dermatitis accounts for the majority of cases of industrial dermatosis, in dermatitides generally the allergic form is far more important. The chapter on contactants includes a list of the more common allergens and affords numerous pertinent examples and illustrations. Here we shall deal principally with the question as to whether cutaneous contact allergy in man is based on an antigen-antibody mechanism, along with some comments on the diagnosis and therapy.

⁷⁷ Peck, S. M., Gant, J. Q., and Schwartz, L. *Indust Med* 14, 214, 1945.

⁷⁹ Koch, F. *Med. Klinik* 37: 1100, 1941.

Strauss and Coca²⁶⁵⁴ champion the view that contact dermatitis is the expression of a strictly epithelial hypersensitiveness without however involving antibodies. Among other arguments advanced by Sulzberger⁶⁹ is the point that antibodies capable of sensitizing the skin passively cannot be demonstrated in cases of contact dermatitis with even the very highest degree of sensitivity. It is true that the presence of circulating antibodies—the so called Prausnitz Kuestner antibodies—can rarely be proved although positive results have been reported by Bereng²⁶⁵⁵ Ensbrunner⁶⁵ Bizzozero and Ferrari²⁶⁵⁶ Urbach⁴³ and others. But as the senior writer^{14,3} has shown the presence of cellular antibodies can unquestionably be demonstrated by the Urbach Koenigstein blister content method. There are in all 36 reported instances of successful passive transfer of allergic contact dermatitis presenting in the recipient the clinical and—so far as examined histologically—the microscopic picture of a dermatitis (see p 153). In all of these cases the passive transfer was possible only with the use of the contents of spontaneous blisters or of cantharides-induced blisters raised on the specifically irritated skin site; the response was invariably a late reaction. FIGURES 40 and 41 show the clinical and histologic picture of a dermatitis produced by such passive transfer. The sensitivity can be transferred by this method not only in spontaneously occurring allergic contact dermatitis but also with uniform success in that experimentally produced with 2-4 dinitrochlorobenzene (Mom and Nousseur²⁴⁰ Ballestero and Mom²⁶⁵⁷).

The mechanism leading to the appearance of such contact dermatitis must be regarded as one of true allergization. This view is supported by the fact that the condition can be evoked under suitable circumstances in any human being or animal. It will be recalled that deliberate allergization of the human skin resulted in dermatitis in 100 per cent of the individuals exposed to primin (Bloch) nitrochlorobenzene (Wedroff and Dolgoff¹⁶⁸ Sulzberger and Baer¹⁶⁹ Ballestero and

Mom²⁶⁵⁸) nickel (Schittenhelm and Stockinger) and arsenphenamine (Frei Nathan and Munk). And we may refer again to the allergization of the skins of animals by exposure to nickel (Walthard) to ursoil (R. L. Mayer) to potassium persulfate (Urbach Zitzke) to phenylhydrazine (W. Jadassohn) and to other substances (see p 45).

Particularly noteworthy, however, are the ingenious experiments of Landsteiner which show that the mechanism on which the hypersensitiveness of contact dermatitis is based is not different from that of any other allergy—i.e. it is an antigen antibody reaction. Landsteiner and Chase²⁶⁵⁸ were able to allergize guinea pigs to simple chemicals such as picryl chloride and 2,4 dinitrofluorobenzene by intraperitoneal injections of conjugates made by combining the chemicals with homologous erythrocyte stromas *in vitro* and to produce anaphylactic death by injection of this mixture—thus unequivocally demonstrating the formation of specific antibodies. In animals similarly prepared epidermal application of the same chemicals called forth a typical contact dermatitis. These authors thus showed that a single allergenic agent can produce either contact dermatitis or classic anaphylaxis thereby proving the basic identity of the two reactive mechanisms. Landsteiner's experiments also serve to explain how the clinical picture of contact dermatitis can be elicited from within by ingestion or injection (e.g. in cases of hypersensitiveness to quinine mercury methenamine arsenicals or chloral hydrate). This observation impelled Sulzberger to use the term contact type dermatitis rather than contact dermatitis.

On the basis of all the facts presented we hold that allergic contact dermatitis is based on the presence of cellular antibodies in the skin. For the purpose of passive transfer they may be rather readily obtained by means of the blister method. One of the reasons why it is so seldom possible at present to demonstrate an antigen antibody reaction in contact dermatitis is that the antigen usually consists of a hapten (e.g. a simple chemical) conjugated with altered skin protein. With

²⁶⁵⁴ STRAUSS H. W. and COCA A. F. *J. Immunol.* 33: 215, 1937.

²⁶⁵⁵ BERENG F. *Dermat. Wchnschr.* 108: 216, 1939.

²⁶⁵⁶ BIZZOZERO E. and FERRARI A. V. *Giorn. ital. dermat. e f.* 72: 3, 1931.

BALLESTERO L. H. and MOM A. M. *Ann. Allergy* 3: 43, 1945.

²⁶⁵⁸ LANDSTEINER K. and CHASE M. W. *J. Exper. Med.* 73: 431,

out employing this complete antigen, it is naturally impossible to demonstrate an antigen-antibody reaction.

However, it cannot be expected that every attempt to demonstrate antibodies—even in cases presenting definitely allergic phenomena—will necessarily be successful, but, as Doerr has pointed out, unequivocal results in a number of cases of a given type of hypersensitivity are adequate proof of the allergic nature of the syndrome in question. On the other hand, as shown above, a contact dermatitis may be toxic and not allergic in origin. Moreover, toxic phenomena probably play a part in many instances of allergic contact dermatitis. For these reasons, the etiology must be proved in every single instance, either by means of patch tests or by appropriate avoidance and re-exposure trials.

Allergic contact dermatitis is almost invariably acquired as a monovalent hypersensitivity. This is gradually transformed, as a result of further allergization, into a polyvalent hypersensitivity, which in turn is finally superseded by a state of complete loss of specificity, in which the skin becomes nonspecifically hypersensitive. This state may properly be termed pathergic contact dermatitis.

However, this concept must not be called upon to justify the assumption that every dermatitis due to chemical or physical injury is primarily allergic. In other words, one is not entitled to refer to "polyvalent" allergy as a convenient explanation of every case. Nor is a given case automatically to be regarded as an allergic dermatitis just because the patient manifests some other allergy (e.g., to a food), for the dermatitis is not necessarily related to the known hypersensitivity. The presence of such a food allergy may, at most, be interpreted as an indication of the organism's readiness for allergization—a general predisposition that may also favor the development of an allergic contact dermatitis.

Just as in toxic contact dermatitis (see p 693), so too in experimentally produced allergic dermatitis, the acid-base balance of the body seems to influence the cutaneous reactions. According to Mom,²⁶⁵⁹ an alkalinizing dietary regimen favors the appearance of

severe cutaneous lesions, with a short reaction time and marked subjective symptoms, after experimental sensitization with 2,4-dinitrochlorobenzene. Moreover, distant reactions or flares of present or previous dermatitic areas or of skin tests were noted. On the other hand, an acid regimen diminished, delayed, or even prevented the production of inflammatory cutaneous reactions. However, this question is not entirely settled on account of the contradictory results described on page 67.



FIG 308 ALLERGIC CONTACT DERMATITIS DUE TO QUININE IN HAIR LOTION

The pictures of acute, subacute, and chronic dermatitis (Figs 308, 309, 310) are too well known to require any description here. The outstanding characteristic is the polymorphism of the efflorescences, the irregular, circumscribed, and intensely pruritic plaques are composed of inflammatory erythematous papulovesicular individual lesions accompanied by oozing or crusting, according to the phase in which the dermatitis happens to be. Corresponding to the inflammatory changes in the epidermis and in the papillary body, the histologic picture presents an intra- and intercellular edema, spongiosis, acanthosis, and parakeratosis in the epidermis, along with acute

²⁶⁵⁹ Mom, A. M. - *Rev. argent. dermatosis* 26: 419, 1942



FIG 309 ALLERGIC CONTACT DERMATITIS DUE TO DYE (PARAPHENYLENE AMINE) USED BY FURRIER



FIG 310 ALLERGIC CONTACT DERMATITIS IN MACHINIST DUE TO ABRASIVE (CARBORUNDUM) IN GRINDING WHEEL

Patch test with this substance as positive in patient but negative in three controls

hyperemia exudate and infiltration in the cutis. In chronic forms the skin becomes thickened and lichenified and is often broken by painful fissures. As a result of scratching and other forms of injury a secondary infection may ensue.

In the beginning the dermatitic manifestations are confined to the skin area directly exposed to the effect of the allergen (FIG 311) later however there is quite frequently a more or less extensive spread of the lesions. This may result either from the carrying of traces of the antigen to other skin sites by



FIG 311 ALLERGIC CONTACT DERMATITIS DUE TO DYE IN SOCKS

means of the hands and clothing or from auto-sensitization. Miescher²⁸⁵⁰ has speculated on a third mechanism mediated by a chemical reflex.

Since the location of the primary site of eruption is an important clue to the possible etiologic agent a list of the more common localizations is presented in Table 38.

Inasmuch as allergic contact dermatitis can not be differentiated on clinical or histologic grounds from toxic contact dermatitis the differentiation must depend as outlined above on the reactions to the appropriate patch tests. A useful table of the concentrations and vehicles to be used for this purpose will be found in the Appendix.

Moreover it is sometimes difficult to distinguish between this condition and neurodermatitis. As an aid in differential diagnosis Sulzberger⁷ recommends the so called differential diagnostic skin test method. This

TABLE 58—Common Causes of Allergic Contact Dermatitis according to Primary Localization

Original Site of Eruption	Sources of Common Allergens
Scalp and forehead	<i>cosmetics</i> shampoos, wave-sets, rinses, bleaches, hair oils, hair tonics, hair dyes, scalp lotions, perfumes, eyebrow pencil <i>headgear</i> hats (felt, dyes), hatbands, sweatbands, bathing caps, wigs, combs <i>medications</i> ointments, lotions <i>miscellaneous</i> hair curlers, hairpins
Eye lids	<i>cosmetics</i> eyelid ointments, eye shadow, eye washes, eyebrow pencils, mascara, scalp or face creams, lotions, tonics, nail polishes, hair dye, shaving creams, face powder; wave set lotions, perfumes <i>medications</i> eye remedies, nasal sprays, nose drops, scalp preparations, ointments <i>miscellaneous</i> spectacle rims, orange skin, carbon paper, soap powders, plants, pollens, insect sprays, gaseous substances, cleaning fluids, benzene, dusts
External ear	<i>medications</i> medicinal instillations and applications <i>cosmetics</i> hair and scalp preparations, perfumes <i>miscellaneous</i> earrings, eeglass temples, earpieces—lacquer, plastic, metal—on dictaphones, radios, hearing devices, ear muffs
Nose and nasolabial areas	<i>cosmetics</i> nail polishes, perfumes <i>medications</i> nose drops, ointments, sprays <i>miscellaneous</i> handkerchiefs, paper tissues
Lips and circumoral region	<i>cosmetics</i> lipstick <i>toilet articles</i> mouth washes, gargles, tooth pastes, tooth powders, tooth brush <i>foods</i> fresh fruits, raw vegetables, dyes in foodstuffs <i>miscellaneous</i> mouthpieces of musical instruments, dentures, pipes, cigarettes, cigarette holders, drugs, chewing gum
Face and chin	<i>cosmetics</i> face lotions, creams, powders, hair lotions, mustache wax, rouge, soaps, other cleansing agents, nail polishes, perfumes, after-shave lotions, secondary contact with cosmetics used by other sex <i>medications</i> ointments, lotions <i>miscellaneous</i> plants, spectacle pads or rims, gas masks, gloves
Neck	<i>apparel</i> silk and woolen scarves, furs, dyes and finishes in clothes and furs, collars, collar buttons, necklaces <i>cosmetics</i> hair dyes, wave sets, hair rinses, perfumes, facial cosmetics, nail polishes, scalp preparations <i>miscellaneous</i> plants, cleaning fluids, blankets
Axillae	<i>cosmetics</i> deodorants, anhidrotics, depilatories, shaving soaps <i>clothing</i> dress shields, dyed fabrics, dry-cleaning fluids (remaining in clothing)
Trunk	<i>clothing</i> day or night apparel (wool, rayon, silk, cotton, dyes, finishing resins); bathing suits, brassieres, girdles, sanitary belts, zippers <i>miscellaneous</i> dusting powders, soaps, plants
Arms and forearms	<i>clothing</i> wool, rayon <i>metals</i> wrist watches, bracelets, glove clasps <i>miscellaneous</i> leather or plastic wrist watch straps, jewelry, lacquer, plants, table wood, lacquer and varnish, cosmetics
Hands	<i>chemicals</i> any used in professions, trades, and avocations, particularly dyes, turpentine, antiseptics, polishing waxes, varnishes, lacquers, cleaning agents, soaps <i>cosmetics</i> nail polishes and removers <i>miscellaneous</i> rubber and leather gloves, newspapers, toys, leather and plastic handles and wheels, plants, jewelry
Groin and genitals	<i>toilet or body articles</i> contraceptives, douches, enemas, drugs (e.g., mercury for pediculosis pubis), menstrual pads, toilet tissue, straps, trusses, supporters, clothing dyes and finishes <i>miscellaneous</i> plants
Thighs and legs	<i>clothing</i> apparel, garters, garter clasps, stockings (nylon, rayon, silk, wool, dyes, finishing resins), metal or plastic on girdles, dry-cleaning fluids, theater seats <i>miscellaneous</i> contraceptives, depilatories, articles in pockets (coins, keys, match boxes, matches, lighters), oil and dusts in work trousers, toilet seats (disinfectants, dyes), plants
Feet	<i>clothing</i> socks, stockings; shoes, shoe linings, shoe polish, tanning agents <i>miscellaneous</i> fungicides, foot powders

differs from etiologic skin testing in that the object of the former is not to discover the cause of the dermatosis but to determine whether the hypersensitiveness is an epithelial or a cutaneous vascular one. When there are several positive patch tests and no wheal reactions to scratch tests the implication is that the case is one of allergic contact dermatitis whereas when the patch tests are negative and the scratch tests positive the diagnosis tends toward neurodermatitis. The occurrence of positive reactions to epidermal as well as cutaneous tests points to the possibility of a combination of contact dermatitis and neurodermatitis. On the other hand negative results with both test methods makes a diagnosis of either form highly improbable and favors the probability of a seborrheic dermatitis or a drug eruption or of some other dermatosis not associated with positive skin tests. Sulzberger suggests that the differential diagnostic patch test be performed with

Nickel sulfate 5% in water
Sodium arsenate 10% in water
Ammoniated mercury 5% in petrolatum
Potassium dichromate 0.5% in water
Iroca ne 2% in water
Formalin 5% in water
Potassium iodide 50% in petrolatum
Paraphenylenediamine 2% in petrolatum
Poison ivy extract diluted 1:5000 with acetone
Turpentine 50% in olive oil
Tincture of pyrethrum as is

Common inhalant food and pollen proteins are used for the scratch tests.

It is occasionally difficult to differentiate contact dermatitis particularly of the hands and feet from fungous infections. While no conclusive criteria are available certain characteristics of morphology and localization are of definite assistance in the differential diagnosis. Thus in contact dermatitis from shoes leather or dye the interdigital spaces are not affected instead the lesions develop where friction or close contact with the shoe takes place—i.e. on the tops of the toes (especially first toe) the dorsal aspect of the foot the instep and the heel. The various contactants which cause dermatitis of the feet are discussed on pages 388 and 402. The situation is further complicated by the fact that contact dermatitis from footwear may appear as a

complication of fungous dermatitis or of dermatitis due to local therapeutic agents. According to Sulzberger the vicious triad of foot dermatitis consists of hypersensitiveness to components of footwear hypersensitiveness to topical medicaments and infection with fungi cocci and other microorganisms. All three types of mechanisms must be considered in every case and often two or all three will be found to share the blame. Hopkins et al.²⁶⁶¹ found that nonmycotic intertriginous lesions of the toes were due to infection by *Staphylococcus aureus* or to sensitization to *S. aureus* shoe polish fungicides antiseptics and similar sensitizing substances. Weidman and his coworkers²⁶⁶² likewise concluded that while fungi cause the majority of intertrigos of the toes bacteria and sensitization are responsible for a considerable number. The significance of chemical abuse of the skin of the feet—often due to self applied remedies—in initiating or maintaining dermatitis pedis was recently stressed by Underwood et al.²⁶⁶³ Even in those cases in which the contact allergen is contained in the footwear the discovery of the actual causal ingredients and the selection of footwear which does not contain these ingredients and which will be tolerated often present a most difficult tedious and sometimes impossible task.

With regard to the hands a dermatitic reaction is likely to be a dermatophytid when all three of the following criteria are fulfilled (1) presence of fungi in the foot lesions (2) a preceding exacerbation of the mycotic infection of the feet and (3) a strongly positive trichophyton reaction. To these differential features Peck, Botnick and Schwartz²⁶⁶⁴ add the following (4) Dermatophytids are more frequently seen on the palms and on the flexural portions of the sides of the fingers and are usually symmetric and tend to appear in showers while contact dermatitis is most often seen on the dorsa of the hands and is rarely symmetric. (5) Removal of the patient from contact with known or suspected

²⁶⁶¹ HOPKINS J G, HELLEGAS A B, CAMP E, LEDIN R B and REINEL G. *Bull U S Army Med Dept* June 1944 No 17 p 42

²⁶⁶² WEIDMAN F D, EMMONS C W, HOPKINS J G and LEWIS G M. *J A M A* 128 805 1945

²⁶⁶³ UNDERWOOD G B, GAUL L E, COLLINS E and MOSBY M. *ibid* 130 249 1946

contactants will not influence a trichophytid; conversely, the treatment of a primary fungous infection should show some evidence of improvement of the lesions suspected of being trichophytids even if occupational exposure is continued. (6) If patch tests with suspected sensitizers are positive in the presence of an active fungous infection and of a positive trichophytin test, there is the possibility of a combination of an "id" and an allergic contact dermatitis. The morphologic characteristics of both conditions have been thoroughly described by Downing.²⁶⁴ Contrariwise, when the foci of the feet are quiescent and trichophytin calls forth little or no reaction, it is not very probable that the manual dermatosis is a trichophytid (Sulzberger⁴). However, the differentiation can often be properly established only by a trained dermatologist.

The question as to whether a dermatophytid predisposes to contact dermatitis has been discussed on p. 478.

Therapy

The treatment of allergic contact dermatitis, even in cases in which the contactant has been identified, is still a problem. Some authors (Gougerot and Blamoutier; Riehl, Jr.; Blumenthal and Jaffé; Maisel; Urbach) have reported success with epicutaneous hypersensitization. This method consists in epidermal application of the causative allergen in increasing concentrations on gradually enlarged skin areas; first a local and ultimately a general state of unsensitiveness can be achieved in this way (p. 205). Instead of epidermal application, injections with antigen-containing salves or baths in antigen solutions may be tried.

Moreover, the intramuscular method (p. 204) has been gaining in favor in the past few years. The antigen is suspended in sterile oil: this procedure, it is claimed, has the advantage of delaying resorption, and consequently of prolonging the effect. Injections of this kind are not to be given more frequently than once a week. In this connection mention should be made of intramuscular injection of plant oils—a method that has its advocates as well as its opponents. While some authors claim good results with it in the treatment of

contact dermatitis due to the oils of ivy, ragweed, chrysanthemum, gaillardia, tulip, and other plants, another group, including Brunsting and Williams²⁶⁵ and Greenberg and Mallozzi,²⁶⁶ reported failures. Sulzberger tried to explain these differences by the assumption that the lowering of sensitivity that follows the injection suffices to prevent dermatitis only under conditions in which the natural response is slight or moderate—but does not prevent the development of clinical manifestations under conditions of massive exposure. He suggests trying a suspension of water-soluble excitants in an oily vehicle.

Another approach is subcutaneous deallergization, consisting in the administration of a weaker concentration in the morning, and a stronger one in the afternoon. In this manner the senior author was able to deallergize a number of patients with severe cases of contact dermatitis due to oickel.

As demonstrated by Schamberg, Strickler, Shelmire, Urbach, and others (see p. 380), oral methods are often effective in dermatitis due to poison ivy, poison oak, and other plants. J. Jadassohn and Perutz used the oral route in cases of allergy to mercury and turpentine, respectively.

By and large, however, the only way to prevent recurrences is by avoiding contact with the allergen. In this connection, the important question arises as to whether or not this leads to a real cure. Thomas²⁶⁷ has reviewed a series of cases of industrial dermatitis from the standpoint of the duration of the sensitivity, and has come to the conclusion that, once established, allergic hypersensitiveness—as expressed by the appearance of contact dermatitis on re-exposure—is usually permanent. Moreover, his analysis indicates that there is a decided tendency for the hypersensitiveness to broaden and to include substances apparently unrelated to the original sensitizing agent. The views expressed by Thomas are now shared by most authorities. Experimentally, these findings have received support from the work of Burckhardt,²¹⁷ who demonstrated that guinea pigs sensitized to turpentine were still hypersensi-

²⁶⁵ BRUNSTING, L. A., and WILLIAMS, D. H. *ibid.* 106, 1333, 1936.

²⁶⁶ GREENBERG, S., and MALLOZZI, E. D. *Arch. Dermat. & Syph.* 42, 250, 1940.

²⁶⁷ THOMAS, E. W. *St. Thomas's Hosp. Rep.* 2, 24, 1937.

²⁶⁴ DOWNING, J. G. *ibid.* 125, 196, 1944.

tive when retested two and a half years later Miescher,²⁶⁶⁸ on the other hand, expressed a dissenting opinion based on the results of follow up examinations he found that of patients who had avoided contact with the allergen from two to three and a half years, 91 per cent were clinically cured, in 69 per cent of the cases it was possible to demonstrate a complete cure, as proved by negative patch tests. The fact that the hypersensitivity disappeared in so many cases suggested to him that allergy is not a "fixed" quality, and that the sensitization in allergic contact dermatitis may be of limited duration.

Whether or not the cause of contact dermatitis is known in a given case, *symptomatic* measures must be undertaken to alleviate the intense itching that is the most distressing complaint, and to combat the local symptoms such as oozing, crusting, and fissuring. For this purpose, soothing wet dressings and lotions are to be prescribed. Since the use of soap will nearly always exacerbate a contact dermatitis, whether or not it is due to this substance, washing should be interdicted except by means of soothing compresses, or with soap substitutes (see p 697), when tolerated.

Dressings—Compresses should be applied three times daily for one hour, during which time they should be changed every eight or ten minutes. Best suited for this treatment are boric acid, 3 per cent aqueous solution, Burow's solution (liquor aluminum acetatis), diluted 1:20 with water, solution of aluminum subacetate (liquor aluminum subacetatis), diluted 1:30 with water, resorcin, 2 per cent aqueous solution, potassium permanganate, 1:5,000 aqueous solution, tannic acid, 2 per cent aqueous solution, and silver nitrate, 1:10,000 aqueous solution.

Lotions—Calamine lotion (without phenol or menthol) is recommended, as well as the following formulas:

	Gm. or Cc.	
R ₁ Zinc oxide		
Talc	\overline{aa} 20.0	\overline{aa} 3v
Glycerin		
Water	\overline{aa} 30.0	\overline{aa} f 3i
(For skin color, add neutracolor)	(3.0)	(gr xlvi)

Sig. Paint on affected parts three times a day

Ten to 30 per cent olive oil may be added, if desirable.

Ointments—Zinc oxide ointment USP may be used or the following:

	Gm. or Cc.	
R ₁ Boric acid 1 per cent solution		
Anhydrous lanolin	\overline{aa} 40.0	\overline{aa} 3x
Petrolatum	20.0	5v

Sig. Apply twice a day

Pastes—Zinc paste NF may be employed alone or to it may be added, depending on whether the dermatitis is subacute or chronic, one of the following preparations: liquor carbonis detergens, 3 to 10 per cent, crude coal tar, 0.25 to 2 per cent, ichthyol, 3 to 10 per cent. (Further information may be found in the excellent monograph *Dermatologic Therapy*, by Sulzberger and Wolf²⁶⁶⁹.)

In cases presenting severe and widespread lesions, an attempt should always be made to reduce the allergic reactivity along nonspecific lines. This can be done with drugs tending to lower the degree of sensitivity, such as calcium (10 cc of 10 per cent calcium gluconate given intravenously, or 1 tablespoonful of the powder in water three times a day by mouth), or Bellergal, a preparation containing belladonna, gynergen and phenobarbital ($\frac{1}{2}$ to 1 tablet three times daily). Strickler²⁶⁷⁰ has recently advocated intravenous administration of sodium thiosulfate every day or two for a series of 5 injections. The mechanism of its effect is not known.

Another approach is an appropriate diet. Thus, the writers have obtained satisfactory results in the management of the acute oozing form of allergic dermatitis by use of the French milk regimen. In this the entire daily diet during the first two days consists of 1 liter of milk plus 1 liter of distilled water, it is ad visable to have the patient stay at home during this period. During the following three days, the patient is kept on a salt poor diet. There is usually a loss in weight ranging from 1½ to 2 Kg. (approximately 3 to 4 pounds). The value of a low-salt diet was confirmed by the observations of Ballestero and Mom.²⁶⁷¹

²⁶⁶⁸ SULZBERGER, M. B. and WOLF, J. *Dermatologic Therapy in General Practice*, ed. 2. Chicago: Yr. Bk. Pub. 1942.

²⁶⁶⁹ STRICKLER, A. *Arch. Dermat. & Syph.* 50: 251, 1944.

²⁶⁷⁰ BALLESTERO, L. H. and MOM, A. M. *Rev. argent. dermatosis* 26: 1115, 1942.

in experimental allergic contact dermatitis in human subjects, since the course, as well as that of existing dermatoses, was favorably influenced and the reactive manifestations considerably decreased.

The intense pruritus is best managed by administration of sedatives such as phenobarbital (0.015 to 0.030 Gm., or $\frac{1}{4}$ to $\frac{1}{2}$ grain, three times daily), or calcibronat (1 teaspoonful of the granules, three times daily) during the daytime, and of appropriate soporifics (e.g., seconal, 0.090 Gm., or $1\frac{1}{2}$ grains) at night. Pipes²⁶⁷² recommended thiamin as an adjunct in the control of the itching: 100 mg is given subcutaneously daily for two or three days, followed by oral maintenance doses of 50 to 75 mg., depending on the course of the dermatitis. Pruritus can also be somewhat relieved, although only temporarily, by roentgen irradiation. The writers advise, however, that no more than three treatments be given (75 r unfiltered, or 100 r through a 0.5 mm. aluminum filter, at intervals of one week).

The secondary infection which so frequently complicates contact dermatitis, prolonging the weeping and delaying healing, usually responds to appropriate measures which should in such cases be given precedence in the treatment. The promising method of combined tyrothricin wet dressings along with penicillin intramuscularly or orally was recently advanced by Vaisberg.²⁶⁷³

3. ALLERGIC DERMATITIS (FROM WITHIN)

Numerous cases have been reported of subacute and chronic dermatitides (other than neurodermatitis) due to foods. Thus, Hazen²⁶⁷⁴ observed the case of a 19 year-old girl with chronic dermatitis, from which she had suffered uninterruptedly since her first year of life, with the exception of one period during which she lived on a small island where milk was not available. Experimental investigation revealed that ingestion of minute traces of cream could elicit the skin manifestations, while the patient remained free as long as milk was strictly avoided. Ramirez²⁶⁷⁵ reported a case of dermatitis of the hand in a

patient who ate bananas every morning; the skin involvement disappeared when the patient refrained from eating this fruit, but promptly reappeared when he again ate it. Ratner²⁶⁷⁶ described dermatitides due to ingestion of egg protein and of milk, Grenet and Clément,²⁶⁷⁷ cases involving bread, Chargin,²⁴³³ flour; and Kipp,²⁶⁷⁸ rye bread. Similarly, Rowe,²¹⁰ employing his elimination diet method, repeatedly demonstrated both wheat and milk to be causes of dermatitis. Hopkins and Kesten⁸¹¹ reported cases due to chicken and venison, respectively. Vallery-Radot and Heimann¹⁸⁷³ achieved complete cure of a dermatitis that had persisted since early childhood by eliminating potatoes from the diet. Tyson observed dermatitides due to ingestion of oranges; Spitzer, cases due to strawberries. Lastly, mention should be made of observations reported by Adelsberger and Munter¹⁰⁶⁹; fruit and grain dealers of both sexes, who had been allergized to fruit or flour by their occupational exposures, subsequently developed an alimentary allergy expressed by dermatitis (sometimes with asthma or angioneurotic edema). The senior writer made similar observations among lemon sorters, and Schoenhof among asparagus workers.

Of the writers' own cases of dermatitis due to nutritive allergy, a few appear to be worthy of special mention. One is of particular interest because it afforded the senior author, in collaboration with Fasal,⁴⁶³ the opportunity of advancing the first recorded experimental proof that there is such a thing as nutritive-allergic dermatitis, by fulfilling all of the requirements considered necessary for a scientific demonstration of an allergic etiology.

The patient, a 22-year-old woman, had been suffering for eleven months from chronic eczematous skin disease and intense pruritus on the back and sides of the neck, on the extensor aspects of both thighs, and elsewhere. Since the history included mention of an aversion to eggs, this item was excluded from the diet, whereupon the skin improved. Then the patient was given two eggs. Within an hour she began to complain of unbearable itching, and simultaneously the dermatitic manifestations, which had almost disappeared, reappeared at all the former sites. Strict elimination of eggs from the diet resulted in complete cessation of the pruritus and marked retrogression of

²⁶⁷² PIPES, D. M. Letters, Internat. Corr. Club of Allergy, Series 5 41, 1945

²⁶⁷³ VAISBERG, M. Ann. Allergy 3: 451, 1945

²⁶⁷⁴ HAZEN, H. H. Arch. Dermatol. & Syph. 19: 121, 1928.

²⁶⁷⁵ RAMIREZ, M. Ibid 2: 365, 1920

²⁶⁷⁶ RATNER, B. M. Clin. North America 6 815, 1922

²⁶⁷⁷ GRENET, H., and CLÉMENT, R. Bull. et mém. Soc. méd. d. hôp. de Paris 47: 514, 1923

²⁶⁷⁸ KIPP, R. Med. Welt 8 1765, 1934

the inflammatory lesions within forty-eight hours. Oral administration of egg repeatedly and with effect



FIG 312 PASSIVE TRANSFER OF HYPERSENSITIVENESS TO EGG WHITE BY MEANS OF BLOOD SERUM FROM PATIENT WITH EXTENSIVE DERMATITIS DUE TO THIS ALLERGEN

Eczematous reaction appearing after 26 hours

That this case—as one of nutritive allergic dermatitis—as most conclusively demonstrated however by the fact that it was possible to transfer the patient's dermatitis to a recipient who had previously responded negatively to a test for hypersensitivity to egg. FIGURE 312 shows the dermatitic reaction of the recipient twenty-six hours after the injection. At this time the cutaneous manifestations elicited by the test consisted of a sharply defined erythematous and elevated site made up of numerous minute papules and pinpoint sized vesicles. Subjectively there was intense pruritus. Histologic examination (FIG 313) revealed all the features of a dermatitic reaction (spongiosis of the epithelium, edema of the papillary body, and leucocytic infiltration around the papillary vessels).

The therapy employed in this case was administration of one egg daily preceded by egg propeptan for a period of fourteen days. Since neither the pruritus nor the dermatitis reappeared, the patient was given egg without propeptan in small quantities slowly increasing from one tenth of an egg to two eggs daily. When the patient was reexamined six months later she was able to eat eggs and was completely free of symptoms.

Another noteworthy case again indicates the unreliability of direct skin testing and the necessity of employing other diagnostic methods.

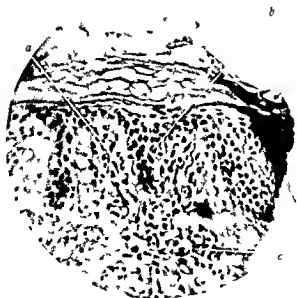


FIG 313 PHOTOMICROGRAPH OF ECZEMATOUS REACTION TO PASSIVE TRANSFER

Same case as in Fig 312 (a) spongiosis (b) edema of papillary body (c) perivascular infiltration

regularly elicited the appearance of the cutaneous symptoms while intracutaneous injection even of concentrated egg white evoked no local reaction.

A 37-year-old man had suffered for ten years from a recurrent oozing dermatitis apparently in association with a jaundice of long duration. The skin condition

always became definitely worse when he was constipated, and especially after eating meat, particularly pork, at such times. In view of the marked eosinophilia (11 per cent), he was given treatment designed to combat the intestinal irregularity, and was put on a strict propeptan diet (see p 217). As a result, the skin manifestations, which had resisted the usual local treatment, promptly showed improvement. On different days the patient ate veal, beef, and pork—and ingestion of any of these meats invariably elicited intense itching and an oozing dermatitis. However, the same quantities of the meats preceded by 2 or 3 specific propeptan tablets were tolerated perfectly, except for slight subjective complaints after eating pork. Intracutaneous tests with extracts of all the meats were entirely negative. On the other hand, passive transfer, with pork extract as the antigen, was successful, by both the Prausnitz-Kuestner and the Urbach-Koenigstein methods. It is, however, interesting to note that the Prausnitz-Kuestner reaction was positive only after twenty-four hours.

Finally, we may mention the case of a boy of 3 years whose dermatitis began to improve only after we had found horse meat, eaten in the form of sausage, to be the allergen responsible. The discovery was made by means of the propeptan method. Elimination of this food from the patient's diet was followed by cure.

However, a nutritive dermatitis is by no means necessarily due to an animal or vegetable protein. The present writers have encountered several cases in which it was possible to demonstrate that table salt and various spices were the allergizing agents. Wittich has even observed a male dog which developed severe dermatitis of the face, neck, and some parts of the body as a result of eating a canned prepared brand of dog food containing fish oil. This cleared up entirely when he was placed on a diet of ground beef, bread, and milk. The dermatitis recurred when he went back on the canned dog food, but again disappeared when it was eliminated.

Another but relatively small group of internally caused allergic dermatitides consists of those due to drugs taken by mouth. Kierland and Brunsting²⁶⁷⁹ apply the name "dermatitis medicamentosa" to drug eruptions that result when the sensitized cutis reacts to a drug protein conjugate formed after the drug is absorbed. The rôle of the hematogenous route in the production of this condition was first

demonstrated by Bloch.²⁵⁹⁶ He succeeded in producing typical dermatitis experimentally by the intravenous injection of potassium iodide and of methenamine, as well as by oral administration of emetine. The senior writer subsequently reported cases of dermatitis following oral administration of quinine, resorcin, and salicylic acid.

The syndrome of "atypical lichen planus," occurring in troops in the southwest Pacific area, is considered by Livingood and Dieuaide²⁶⁸⁰ to be due essentially to hypersensitiveness to atabrine, although other factors may contribute to the onset and localization of the lesions. However, convincing evidence of drug allergy in these cases is not presented. Goldberg²⁶⁸¹ found that administration of atabrine did not cause exacerbations of the lichenoid dermatosis. An excellent clinical description of the three types of this new cutaneous syndrome was contributed by Nisbet.²⁶⁸²

It has frequently been observed that dermatitides caused by agents taken orally are of the erythematous type, while allergens acting through external contact tend to produce eczematous manifestations. This difference in type of reaction has been explained by the writers on the basis of the quantitative differences in the amounts of allergen absorbed as a result of the different forms of exposure. This would seem to confirm Bloch's assumption that the degree of concentration of the allergen determines whether the response is an erythematous or an eczematous one. He arrived at his explanation after performing the following experiment. A patient hypersensitive to resorcin reacted with a severe weeping dermatitis to the application of resorcin compresses. Administration of 0.5 Gm (7½ grains) of resorcin by mouth, on the other hand, elicited erythematous skin manifestations; a dose of 1 Gm (15 grains), however, evoked a reaction in the form of an eczematous eruption.

In addition, the group of allergic dermatitides of internal origin includes the numerous observations of dermatitis appearing after intravenous injection of arsphenamine, gold, and

²⁵⁹⁶LIVINGOOD, C. S., and DIEUAIDE, F. R. *J. A. M. A.* 129: 1991, 1945.

²⁶⁸⁰GOLDBERG, L. C. *Ibid.* 130: 775, 1946.

²⁶⁸²NISBET, T. W. *Arch. Dermat. & Syph.* 52: 221, 1945.

²⁶⁷⁹KIERLAND, R. R., and BRUNSTING, L. A. *Proc. Staff Meet., Mayo Clin.* 17: 28, 1942.

other drugs. Lastly it also properly embraces the cases caused by *endogenous allergens*—e.g. menstrual dermatitis (see section on endogenous allergy).

The treatment of dermatitis originating from absorption of either food or drugs is comparatively easy. Skeptophylactic methods are used. Small amounts of the allergenic food (or preferably of specific propeptans) or of the respective drugs are given by mouth three quarters of an hour before ingestion of larger amounts of the given food or drug. In this manner deallergization is achieved. A number of authors including Brandt, Chajes, von Eiselsberg, Hecht, Markin, Reiss, Rusten and Schreus have reported cures following adherence to specific propeptan diets.

4. NEURODERMATITIS

For clinical pathogenetic and therapeutic reasons a distinction must be made between contact dermatitis and the form of dermatitis to be referred to below as neurodermatitis. This condition is in turn to be divided into two subgroups: the circumscribed type (also called neurodermatitis circumscripta chronica, lichen simplex chronicus of Vidal) and the disseminated type (also known as atopic dermatitis of Sulzberger⁴, generalized neurodermite of Brocq, eczema asthmaticum, hay fever complex of Stokes²⁶⁵, *prurigo diathésique* of Besnier and flexural eczema).

SYMPTOMATOLOGY

Circumscribed neurodermatitis is characterized by sharply defined, highly lichenified, infiltrated, hyperpigmented (though in rare instances depigmented), intensely pruritic lesions (FIG. 314) showing a tendency to recur. The sites of predilection are the back and sides of the neck, the dorsum of the hand, the medial aspect of the thigh, and the lateral aspect of the lower leg. This form of dermatitis is practically never encountered in children.

Disseminated neurodermatitis is almost invariably located on the face (FIG. 315) and on the flexural surfaces of the principal joints, particularly the antecubital and popliteal spaces (FIGS. 316-317) and less commonly in



FIG. 314 LOCALIZED NEURODERMATITIS, LICHEN SIMPLEX (VIDAL)



FIG. 315 CHARACTERISTIC APPEARANCE OF NEURODERMATITIS OF FACE

Lichenification of skin and nearly complete loss of eyelashes

²⁶⁵ STOKES, J. H. M. Clin. North America 29, 1931

the inguinal, crural, and axillary folds. In cases of many years' duration, the skin of the face may become thickened and leathery from lichenification, with a color ranging from grayish to brownish-purple, thus producing the appearance of a ghostly mask, moreover, the characteristic absence of eyebrows (FIG. 315), at least laterally, due to rubbing, gives the face an odd expression—so that, all in all,

dition may become secondarily impetiginized, owing to scratching and superimposed infection (FIG. 319). Finally, generalization of the skin manifestations may take place in patients of all ages. The itching in these cases is unhearable and is often relieved somewhat only when the skin bleeds as a result of vigorous scratching. Stokes⁶ calls attention to the fact that the skin of these patients turns

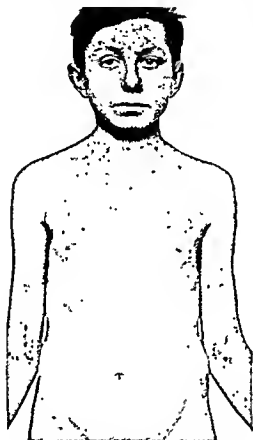


FIG. 316 TYPICAL DISTRIBUTION OF DISSEMINATED NEURODERMATITIS ON FACE, NECK, AND ANTECUBITAL SPACES

most neurodermatitis patients look more or less alike.

In both the disseminated and circumscribed types, the primary lesion usually consists of a skin-colored papule, the center of which is often covered with a bloody crust as a result of scratching due to intense pruritus (FIG. 318). The papules, particularly those in the flexures and on the medial aspect of the thighs, become confluent and form poorly defined plaques; this eventually gives the skin its characteristic coarse appearance. The con-

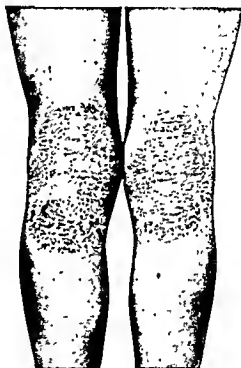


FIG. 317 DISSEMINATED NEURODERMATITIS WITH INVOLVEMENT OF POPLITEAL SPACES

white instead of red upon rubbing or scratching (white or sympathicotonic dermatographism).

It is strikingly common observation that neurodermatitis occurs in conjunction with asthma or alternates with it. In our material (published by Brandt^{76,77}), bronchial asthma was present in approximately one-fourth of all cases of neurodermatitis, while Rost found asthma in one-third of his cases. Baagoe, moreover, encountered neurodermatitis in about 20 per cent of his asthmatics. While we have never observed a regular alternation of the two conditions, it has been reported by Vallery-Radot and Haguénau, Comby, and

⁷⁶ BRANDT, R. *Dermat* 7:tschr 65 330, 1933. *Ztschr f Konstitutionslehre* 17: 225, 1932.

others. Moreover neurodermatitis patients frequently present hay fever and less often importance of a hereditary factor in this disease.



FIG 318 NEURODERMATITIS OF HANDS

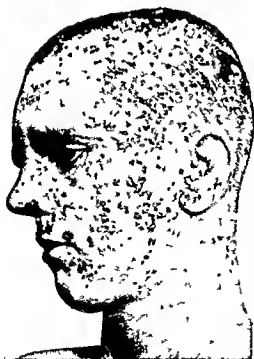


FIG 319 SECONDARILY INFECTED NEURODERMATITIS

migraine. Finally, numerous authorities have reported positive family histories of asthma, hay fever, or migraine in a large percentage of patients—a fact clearly demonstrating the

The relatively frequent occurrence of catarrh in youthful neurodermatitis patients will be discussed in some detail in the chapter on allergic diseases of the eyes.

The question regarding the extent to which the circumscribed and disseminated types are related is still controversial. The facts that the most characteristic features of both are pruritus along with the development of lichenified patches in typical localizations and that transitional and combined forms are frequently observed led J. Jadassohn²⁶² and Tachau²⁶³ to consider the two types as merely related forms. Hull and Sultzberger²⁶⁴ on the basis of their material, however, are of the opposite opinion.

Finally, it should be pointed out that neurodermatitis, particularly in childhood, is very often a direct continuation of infantile dermatitis, chronologically and probably also pathogenetically. At first only the flexures are involved; then approximately in the eighth or tenth year of life the child begins to present the typical picture of neurodermatitis disseminata, with the characteristic involvement of the face. Only rarely do the cutaneous manifestations of neurodermatitis make their first appearance after puberty. In these cases as well as in those dating back to early childhood

²⁶² TACHAU, P. *A. ta dermat. venerol.* 20: 42, 1939.

²⁶⁴ HULL, L. W. and SULTZBERGER, M. B. *A. h. Dermat. & Syph.* 32: 451, 1935.

the entire skin is invariably strikingly dry and strangely brownish-gray in color

PATHOGENESIS

The pathogenesis of neurodermatitis is by no means uniform, nor is the condition by any means necessarily of strictly allergic origin. The term neurodermatitis seems to us to be preferable to other designations, since it most clearly emphasizes the fact that an unstable nervous system, over-reacting to emotional strain, plays a special rôle in this skin disease—even in the numerous cases in which a food or an inhalant can be shown to be the causal allergen. Moreover, this does not in any way negate the fact that heredity is often an important predisposing factor in the causation of neurodermatitis.

While in contact dermatitis the epidermis is the shock structure, in neurodermatitis the blood vessels of the cutis are the shock tissue: in other words, we are here dealing with a vascular-cutaneous hypersensitiveness. This serves to explain the fact that neurodermatitis is very frequently associated with vascular hypersensitiveness in other organs—e.g., asthma, hay fever, and migraine. To determine whether, in a given case, the hypersensitiveness is primarily epithelial or primarily vascular, Urbach has suggested a method described in detail on page 38.

In a small number of cases, it is possible, by the patch test method, to demonstrate that the neurodermatitis is due to some contactant. Thus, Peck²³⁵ and Albert and Walzer²³⁶ reported in children positive epidermal reactions to silk, feathers, goat and cow epithelium, cottonseed, orris root, and ragweed pollen. Frei observed a case of widespread neurodermatitis found to be due to hypersensitiveness to horsehair; Biberstein, a case due to cats; Boström, reaction to fish; Urbach, as well as Herrmann, Sulzberger, and Baer, cases attributable to wool and silk; J. Jadasohn and R. L. Mayer, to ursoil. However, according to Osborne et al.,²³⁷ patch tests are of diagnostic value only if they simulate clinical conditions as closely as possible; better still is an actual trial, such as having the

patient wear a fuzzy sweater or a woolen glove or coat. Since the shock structure in neurodermatitis is constituted by the cutaneous vessels and not by the epidermis, it must be assumed that transepidermal absorption of water-soluble protein allergens takes place. This concept was confirmed by the uniform success achieved by Herrmann, Sulzberger, and Baer²⁰⁶ in obtaining immediate whealing reactions in a series of patients with neurodermatitis by means of injection tests with ordinary protein allergens in special vehicles. It should be emphasized that the tests were performed on clinically normal and intact-appearing skin sites. The reactions appeared within two to five minutes after injection for ten to thirty seconds, and sometimes even earlier. A positive response could be obtained with every allergen to which the same patient manifested a positive scratch test.

A series of observations has convinced Simon^{140, 238, 239} that human dander is an important allergenic excitant of neurodermatitis. While positive intracutaneous and passive transfer tests with this substance have been obtained, they do not reproduce the lesions of the disease. On the other hand, patch tests with human dander are positive in the majority of patients tested, either on uninjured skin or, in some cases, on skin which has previously been scratched, and take the form of an eczematous reaction. Moreover, massage of mixtures of dander in petrolatum or soap solution into the skin produced papules in some subjects. Simon suggests that the predilection for certain skin areas manifested by neurodermatitis is not dependent on hemogenous distribution of allergen or on increased specific sensitivity of these regions, but may be the result of proximity of the affected areas to the scalp and of factors favoring accumulation, solution, and penetration of dander. Such factors include sweating and injury to the skin by scratching. The final evaluation of the importance of human dander in the causation of this disease must await confirmation by independent investigators.

It is generally thought that inhalants are

²³⁵ PECK, S. M. *New York State J. Med.* 34: 957, 1934

²³⁶ ALBERT, M., and WALZER, M. *J. Invest. Dermat.* 3: 119, 1940

²³⁷ OSBORNE, E. D., JORDAN, J. W., and HALLATT, J. J. *New York State J. Med.* 42: 47, 1942.

²³⁸ SIMON, F. A. *J. Allergy* 15: 358, 1944

²³⁹ *Ibid.* *Arch. Dermat. & Syph.* 51: 6, 1945; *South. M. J.* 38: 530, 1945

far more commonly responsible for causing and maintaining neurodermatitis than are contactants. In the former case the allergen is transported to the shock structure by the hematogenous route. Engroan and Wander⁷⁵⁹ described 2 cases in which chronic generalized dermatitis was apparently due to inhalation of horse dander. Rattner and Pusey⁷⁶⁰ demonstrated that a young man's neurodermatitis was definitely due to the perfume used by his wife. Employing the nasal insufflation test, Taub and Zakon⁷⁶¹ and Sulzberger and Vaughan⁷⁶² were able to prove that silk protein, horse dander, and dust were etiologic factors in neurodermatitis. Figley and Parkhurst⁷⁶³ and Sulzberger and Vaughan⁷⁶² have stressed the etiologic importance of silk dresses or silk stockings in severe cases of neurodermatitis. The last named authors reported experiments indicating that the silk allergen could be absorbed by inhalation in sufficient quantity to affect passively sensitized skin sites. Moreover, these authors were able to elicit a flare up of the skin manifestations and a constitutional reaction by means of a dilution of silk protein as high as 1:500,000 using the scratch test technic. In millers, bakers, and others who are occupationally exposed, flour may act as an inhalant allergen. We have mentioned above the case of a 15 year old daughter of a baker who suffered from neurodermatitis from her earliest youth. While skin tests with flour were negative, the nasal test elicited severe constitutional symptoms and asthma in a few minutes followed by an exacerbation of the skin condition persisting for a few days. Correspondingly, if the patient remained away from home for about a week, the skin cleared, only to relapse soon after her return.

Cazort⁷⁶⁴, Rowe,⁷⁶⁵ and Feinberg¹⁶⁰⁰ described seasonal aggravation of neurodermatitis due to inhalation of pollen. Of particular interest in this connection is Feinberg's statement that during a strong wind with unusually high temperatures in November 1938—resulting in an extraordinary number of mold spores in the air—several of his mold sensitive neurodermatitis patients suffered

acute flare up of their dermatoses. The senior author observed a patient with neurodermatitis and pollinosis who always experienced an exacerbation of his skin lesions during the hay fever season or when tested nasally or cutaneously with certain weed and grass pollens outside of the hay fever season. The circumstances justifying the conclusion that pollens and molds are among the causative allergens in a given case are, according to Feinberg¹⁶⁰⁰: a history of seasonal exacerbation, positive reactions to cutaneous tests with the seasonal air borne allergens, demonstration of skin sensitizing antibodies, correlation of fluctuations in intensity of symptoms with the varying air content of pollen and fungus spores, occasional flare up of the dermatitis following injection of pollen or fungus extracts, and improvement in the condition following specific hyposensitization measures.

The reluctance to accept inhalants in general as an important cause of neurodermatitis is due, as Feinberg points out, to the difficulties encountered in associating chronic symptoms with perennial causes. One would naturally suspect that, if the inhalant allergens were seasonal, the correlation between the cause and the skin disease would be more readily apparent.

In perfect agreement with this view is the finding of Rost,²⁶² Sulzberger and Vaughan,⁷⁶² and Rappaport²⁶⁹⁴ that a carefully controlled environment with strict precautions against air borne allergens (use of a so called allergen free room) is of definite value in the treatment of this disease. Hence the good results obtained from simple hospitalization or from a trip to the mountains or seashore. According to Rost it is sometimes enough to have the patient spend his nights in an allergen free room allowing him to continue his regular occupation during the day. In such instances one must then attempt to find the causal allergen in the patient's home. In damp apartments (usually basement or ground floor) the allergen may be a mold. If this is confirmed by appropriate tests, the physician must insist that the patient move to a more suitable residence, for the mold cannot be effectively eliminated. In a number of our own cases, the condition was found to be directly de-

⁷⁵⁹ ENGROAN, M. F. and WANDER, W. G. *Arch. Dermat. & Syph.* 3: 213, 1921.

⁷⁶⁰ RATTNER, H. and PUSEY, W. A. *J. A. M. A.* 99: 1934, 1932.

⁷⁶¹ ZAKON, S. J. and TAUB, S. J. *J. Allergy* 9: 523, 1938.

⁷⁶² CAZORT, A. *South. M. J.* 29: 1022, 1936.

²⁶⁹⁴ RAPPAPORT, B. Z. *J. Allergy* 11: 200, 1940.

pendent upon the patient's place of residence, and correspondingly to benefit from a change of environment. Cazort^{28,29} has emphasized the significance of house dust as an allergen.

In another group of cases, the principal cause of neurodermatitis was found to be hypersensitiveness to foods. Most of the patients in the group were children; however, a number of adults were also included in the writers' material. The most commonly encountered allergens were eggs, milk, flour, fish, and meat. The diagnosis is established by the elimination and trial diet methods.

Not infrequently the very same food which has been found to be an etiologic factor in a given case when ingested, can be demonstrated to cause a flare of the neurodermatitis on contact, or even on inhalation of the odor. In some cases the contact will result in contact dermatitis instead—representing coexistent epidermal and dermal sensitization. Templeton³⁰ reported pertinent cases in which egg and wheat were the offending allergens by both ingestion and contact. Similar observations were made by the senior author (pp. 384 and 667).

However, for every one of the relatively few cases in which it is possible to identify the cause of neurodermatitis, there are dozens in which the causal agent cannot be found, despite the most diligent search.

The question of the importance of endogenous allergens originating in faulty digestion, endocrine dysfunction, and other metabolic disorders has not received adequate study. As a result, there is a marked tendency, in our opinion, to underestimate the importance of endogenous allergens in this connection. The writers believe that they are of considerable importance and that this will eventually be recognized.

Spectrographic analysis of the lesions of neurodermatitis by MacCardle, Engman, and Engman^{35,36} revealed a magnesium deficiency of the skin, although the blood values were normal. However, magnesium deficiency in animals appears to be entirely unrelated, and does not reproduce the disease (Sullivan and Evans^{36,37}).

Perhaps greater in neurodermatitis than in

any other allergic disease is the influence of predisposing factors. Every physician knows that neurodermatitis is somehow dependent, for example, upon seasonal influences, in that the condition often flares in the spring and fall. It is not yet known to what extent these exacerbations are dependent upon disturbances of the endocrine functions or imbalance



FIG 320 NEURODERMATITIS ON BASIS OF BACTERIAL ALLERGY (PYELITIS DUE TO STREPTOCOCCUS)

of the sympathetic-parasympathetic equilibrium. There are numerous indications that at these times of the year an increased irritability of the autonomic nervous system or increased thyroid function is present. Furthermore, mention must be made here of the significance of gastro-intestinal disturbances (hypo-acidity, abnormality of intestinal flora, constipation) and of infections (foci in the teeth, tonsils, gallbladder, and in the pelvis of the kidney). FIGURE 320 shows a patient who had a severe exacerbation of neurodermatitis each time she had a recurrence of pyelitis.

³⁵ MACCARDE, R. C., ENGMAN, M. F., JR., and ENGMAN, M. F.
Arch. Dermat. & Syph. 44, 429, 1941, 46-337, 1942

³⁶ SULLIVAN, M., and EVANS, V. J. *ibid.* 49: 33, 1944

Ehrmann²⁶⁹⁷ reported the complete clearing of lesions following the surgical removal of a chronically inflamed appendix.

As mentioned above marked neuro instability and nervousness are observed in almost every case of neurodermatitis. Emotional disturbances hold a prominent place among the most common immediate causes of attacks in some cases they apparently are the major factor. The skins of such patients will explode under nervous and mental pressure. Stokes²⁶⁹⁸ goes so far as to speak of a personality peculiar to neurodermatitis patients characterized by a deep-seated feeling of insecurity and inferiority, marked lability of physical and mental reactions, higher than average intelligence, tension expressed or repressed restlessness and overdependence. The importance of psychosomatic factors was confirmed by Lynch, Hinckley and Cowan²⁶⁹⁹ who added suppressed resentment to the above personality traits. According to Greenhill and Finesinger²⁷⁰⁰ patients with neurodermatitis exhibit psychoneurotic symptoms more frequently than do control groups and were found to have hostile tendencies, a sense of inadequacy and depressive trends. Moreover a definite correlation was observed between the events which evoked feelings of anger and depression and exacerbations of the skin lesions.

Lastly there are the stigmata that Rost has described as characteristic of neurodermatitis. The glucose tolerance test very frequently yields a strikingly low curve, a finding that has been confirmed in the present writers' experience. According to Huellstrung²⁷⁰¹ a minimal increase in blood sugar follows administration of epinephrine. Furthermore there is an increased tonus of the subcapillary vascular plexus as manifested by the characteristic gray skin color, the white dermographism and the absence of a red halo following intracutaneous injection of the allergen. There is also a tendency toward lowered blood pressure, rapid pulse rates and low white blood cell counts. Ehrmann²⁶⁹⁷

found that one half the patients showed a decrease or absence of gastric acidity while only a few had hyperacidity. As Brandt²⁷⁰² insists—and justifiably in the writers' opinion—neurodermatitis can develop only in peculiarly predisposed individuals. Neurodermatitis patients as a rule are tall and lean with poor muscular development and scanty sweat and sebaceous secretion, moreover signs of constitutional inferiority and family histories of allergy are present in a strikingly high percentage of these cases.

DIAGNOSIS

In general circumscribed and disseminated neurodermatitis present a clearly defined disease picture characterized by a typical distribution, lichenification, intense itching and absence of vesicles. In some instances however it is almost impossible to differentiate between neurodermatitis and certain forms of dermatitis. Thus for example a chronic *eczema en plaque* or a secondarily lichenified contact dermatitis can sometimes barely be distinguished from a circumscribed neurodermatitis. Moreover it is at times extraordinarily difficult to decide whether a given case represents eczematized disseminated neurodermatitis or chronic lichenified dermatitis.

Neurodermatitis must also be differentiated from seborrheic dermatitis which usually starts on the scalp and behind the ears and spreads to the chest. Most important of all however for both pathogenetic and therapeutic reasons is the differentiation between neurodermatitis and contact dermatitis. Table 59 compiled by Garner²⁷⁰³ and Sulzberger²⁷⁰⁴ and expanded somewhat by the writers presents a clear summary of these problems. For details concerning Sulzberger's differential diagnostic skin testing to distinguish between neurodermatitis and contact dermatitis the reader is referred to page 107.

A number of different methods are employed to determine the causal allergen. If the manifestations abate during the patient's stay in an allergen free room (see above) it may well be assumed that the allergen is an inhalant one. Further investigations will then have to be undertaken to ascertain its

* EHRMANN S. A. *Arch. Dermat. u. Syph.* 183: 346, 1922.

* STOKES J. H. *Arch. Dermat. u. Syph.* 42: 789, 1940.

* LYNCH F. W., HINCKLEY R. G. and COWAN D. W. *ibid.* 51: 251, 1945.

* GREENHILL M. H. and FINESINGER J. S. *ibid.* 46: 187, 1942.

* HUELLSTRUNG H. *Monatshefte für Kinderheilkunde* 10: 1, 1939.

* BRANDT R. W. *Zeitschrift für Hautkrankheiten* 48: 98, 1931.

* GARNER L. C. *Med. Clin. North America* 18: 310, 1935.

TABLE 59.—*Differential Diagnosis of Neurodermatitis, Allergic Contact Dermatitis, and Seborrheic Dermatitis**
(based in part on Garner²³ and Sulzberger¹)

	Neurodermatitis	Allergic Contact Dermatitis	Seborrheic Dermatitis
Age of Onset	Usually before 18 years (7 to 20 years)	Any age, usually adult	Late childhood, early adolescence or thereafter
Family History of Allergic Diseases	Usually positive high incidence of asthma, dermatitis, hay fever, urticaria allergic rhinopathy	Negative normal incidence	Negative
Personal History of Allergic Diseases	Usually positive may be associated with or alternate with hay fever or asthma	Negative normal incidence	Negative
Family and Personal History of Seborrheic Conditions	Negative normal incidence	Negative	Positive high incidence of male type of baldness, dandruff, acne vulgaris, greasy and oily skins, pustulous follicles
Antecedant Dermatitis	Infantile dermatitis frequently	Uncommon	Sometimes preceded by seborrheic type of infantile dermatitis
Predisposing Background	Affects dry skin, neurocirculatory instability usual	Favored by ichthyosis, seborrhea, pyogenic and mycotic infections stasis	Dietary excess of oils, fats, alcohol, carbohydrates, disorders of fat metabolism, indigestion, hypothyroidism
Appearance of Unaffected Skin	Often dry, with tendency to hyperpigmentation	Usually normal, sometimes excessively moist, dry, greasy, or keratotic	In some cases, greasy and/or oily, often normal
Common Characteristics of Eruption	Dry, papular, hemihemid, highly pruritic, not sharply demarcated	Acute or subacute, not sharply demarcated, with one or more of erythema, edema, vesicles, papules, scaling, infiltration, and hemihemidification	Diffuse or sharply circumscribed, erythematous, nonvesicular, with greasy scales, little or no pruritus
Localization	Antecubital and popliteal spaces, eyelids, around mouth, sides and back of neck, dorsa of hands and fingers; may be generalized	Wide variations, most commonly onset or principal involvement on exposed areas (face, hands, forearms), flexures rarely	Scalp, forehead, eyelids, nasolabial folds, postauricular, presternal, interstapular, axillary, and pubic regions
Dermographism	Pronounced pale reaction (white dermatographism)	Average expected response	Average expected response
Personality	Usually egocentric, emotionally unstable, overambitious, "poker face"	Average pattern	Average pattern
Duration	Many years, may disappear in 20's or persist for life	Usually disappears on recognition and removal of cause	Usually responds to therapy, may be resistant or recur
Scratch and Intradermal Tests	Few to many positives, often of questionable significance	Usually negative, of no significance	Generally negative

* Combinations of any two or of all three forms may occur, presenting the combined characteristics of the forms concerned

TABLE 59—*Concluded*

	Neurodermatitis	Allergic Contact Dermatitis	Seborrheic Dermatitis
Patch Tests	<i>Usually negative to a series of common eczematogenic allergens except wool and silk</i>	<i>Generally positive to causative agent or to some members of a series of common eczematogenic allergens</i>	<i>Generally negative</i>
Passive Transfer Tests	<i>Often positive with blood serum (Prausnitz Kustner method)</i>	<i>Often positive with blister fluid (Urbach Koenigstein method)</i>	<i>Negative</i>
Character of Allergens	<i>Ingested or inhaled substances either protein or associated with proteins (may be elicited by external contact probably through transepidermal penetration)</i>	<i>Water or oil soluble simple compounds (nonproteins) e.g. dyes, medicaments, products of plants (only fraction), synthetic chemicals etc.</i>	<i>No known allergic basis</i>
Eosinophilia	<i>Often positive</i>	<i>Negative</i>	<i>Negative</i>
Prognosis	<i>Poor for immediate future</i>	<i>Excellent if cause can be ascertained</i>	<i>Favorable under treatment, resistant on scalp with ultimate alopecia</i>
Treatment	<i>Hyposensitization or deallergization, elimination or avoidance</i>	<i>Removal of local cause, topical measures</i>	<i>Dietary, vitamins, anti-infectious and local measures, X-ray</i>

exact identity—silk, feathers, dust, or other inhalant. If the allergen is a contactant, patch tests may be of value, but must sometimes be applied to an area that has been the site of a lesion. If food is suspected of being the allergen, a strict elimination diet must be instituted. Skin tests—especially intracutaneous ones—are in general of no clinical significance. Positive skin reactions and successful passive transfer tests are diagnostically valuable only if external application or internal administration of the suspected allergen causes the objective and subjective symptoms of neurodermatitis to appear, and if these lesions disappear on elimination of the agent. Lastly, it must be mentioned that a negative skin test by no means rules out the possibility of food allergy.

THERAPY

Neurodermatitis is a disease that tries the skill and patience of allergists and dermatologists alike. Since the condition is generally brought on by three principal factors—(1) inhalant, contact, or food allergens, (2) certain predisposing factors (see above), and (3) an unstable nervous system over reacting to emotional strain—all must be combated

and, so far as possible, removed at the same time. Hospitalization is advisable in order to facilitate the efficient performance of all necessary environmental, dietary, and skin tests.

The specific treatment depends, naturally, on the identification of the specific agent. When there is a hypersensitiveness to a contactant, inhalant, or ingestant, exposure to the agent must be eliminated or appropriate hyposensitization measures attempted. This may be accomplished with fairly good results when the causative allergen is dust, silk, feathers, or fungus spores (Fios 321, 322). The use of an allergen free room, as an initial therapeutic measure, has been discussed above. The management of nutritive allergy in infants and children is discussed below (p. 728). The writers have obtained satisfactory results with the propeptan method in cases of nutritive allergy.

Predisposing factors, such as gastrointestinal and endocrine disturbances, as well as focal infections, should be eliminated as carefully as possible. In almost all cases of neurodermatitis, the attending physician is obliged to administer psychotherapy—ruled by good common sense—and directed fully as much to

the patient's family and friends as to the patient himself. The chief purpose of psychotherapy is to lower the psychic tension. This is accomplished by means of recreation, hobbies, change of environment, particularly a sojourn at the seashore, with frequent bathing and sun baths, or ocean voyages. Among the drugs, Bellergal ($\frac{1}{2}$ or 1 tablet three times a day), calcibronat granules (1 teaspoonful three times a day), and triple bromides (0.5 Gm three times a day) have proved themselves to be the most useful.

vious X-ray treatment, it should be covered with gauze spread with the following cold cream before the compresses are applied:

	Gm	
R Boric acid	2 0	$\overline{55}$
Greaseless base	60 0	$\overline{511}$
(Burroughs Well come & Co)		
White petrolatum	q s ad 90 0	q s ad $\overline{511}$

Lotions and ointments used should be free of lanolin since many neurodermatitis patients are allergic to animal fat. Lotions



FIG. 321



FIG. 322

NEURODERMATITIS AND ASTHMA DUE TO HYPERSENSITIVENESS TO FEATHERS AND MILK

FIG. 321 Intracutaneous injection of 0.1 cc of 1 per cent feather extract produced strong local immediate reaction, followed twenty minutes later by attack of asthma. Similar paroxysm called forth by drinking glass of milk.

FIG. 322 Same patient after strict elimination of feathers and milk.

Cases in which a specific cause cannot be found, or that are refractory to specific treatment, must be treated symptomatically. This approach may be divided into local and general measures. Topical dermatologic treatment is of the utmost importance. First of all, the use of soap and water, including bathing, is strictly forbidden. However, ocean baths are an exception to this rule, for they are definitely beneficial when combined with exposure to sunlight. Cold compresses with 2 per cent resorcin, 3 per cent boric acid, or 0.25 per cent aluminum subacetate will provide relief from the enervating itching. If the skin is very dry, owing either to slight ichthyosis or pre-

should contain enough oil to make the skin supple. For example:

	Gm or Cc.	
R Olive oil	20.0-40 0	$\overline{15v-x}$
Zinc oxide		
Talc	\overline{aa} 20 0	\overline{aa} $\overline{5v}$
Glycerin		
Water	\overline{aa} 30.0	\overline{aa} $\overline{f3i}$

Ointments should have the addition of tar, particularly naftalan, or naftex (Lascoff), crude coal tar, or oil of cade:

	Gm or Cc	
R Crude coal tar	3 0-10 0	$\overline{5i-iii}$
Sesame oil	10 0	$\overline{f3iii}$
Zinc oxide		
Talc	\overline{aa} 25 0	\overline{aa} $\overline{5vi}$
Petrolatum	q. s. ad 120 0	\overline{q} s ad $\overline{5iv}$

X ray treatment definitely helps to overcome the itching; it should be used sparingly, however, since it dries the skin, thus initiating a vicious cycle.

Systemic measures include fever therapy with bacterial vaccines such as typhoid vaccine or pyriser. Because of the danger of anaphylaxis, milk injections are not recommended. Good results are often obtained nonspecifically by a complete change of diet, for example, a regimen exclusively of raw fruits and vegetables for from two to four weeks (Figs. 323-324). The beneficial effect of a low salt diet was reported by Ballestero

and metics dyes and primary cutaneous irritants; these do not differ from the condition in adults. Circumoral dermatitis due to contact with foods, particularly vegetables and fruits, also represents an epidermal sensitization. Lastly, mycotic and bacterial dermatoses may also occur; these are easily distinguished clinically from the conditions mentioned and will like wise not be discussed here, since they are not primarily allergic in character. The relative frequency of the various dermatoses can be judged from Hill's²⁰⁴ analysis of 156 cases of so-called eczema in childhood: 103 had infantile dermatitis, 31 contact dermatitis, 11



FIG. 323. NEURODERMATITIS IN CHILD OF 4½ YEARS.



FIG. 324. SAME PATIENT AFTER FOUR WEEKS' DIET WHOLLY OF RAW VEGETABLES AND FRUITS.

and Mom.²⁶⁷¹ The favorable influence of a change of climate (seashore or mountains) has been mentioned above. It must be borne in mind, however, that the relief obtained from these nonspecific measures cannot be expected to persist more than a few weeks—unless in the interim the allergenic agent and the predisposing factors are discovered.

5. INFANTILE DERMATITIS (INFANTILE ECZEMA)

The inflammatory dermatoses of infancy and early childhood, commonly referred to as infantile eczema, may be subdivided into two major groups: infantile dermatitis and seborrheic dermatitis. There are also occasional instances of contact dermatitis due to topical medication, poison ivy, soap, wool, silk, cos-

metics, dyes, and 9 seborrheic dermatitis, nummular eczema, and circumscribed neurodermatitis.

It may be necessary to justify the use of the term infantile dermatitis in place of the designations infantile eczema (Moro²⁷⁰⁵), atopic dermatitis (Sulzberger⁶⁸⁷ and Hill¹⁶⁸), true eczema (Finkelstein⁹), and early exudative eczematoid (Rost). In the discussion of the classification of forms of dermatitis, the reason why the vague designation eczema should be eliminated from medical terminology was made clear. The same consideration led Sulzberger and Hill to suggest the term atopic

²⁰⁴ HILL, L. W. *J. Pediatr.* 20: 53, 1942.

²⁶⁷¹ MORO, E. *Eczema Infantis* and *Dermatitis seborrheica*. Berlin, Springer, 1932.

²⁷⁰⁵ HILL, L. W. *J. A. M. A.* 111: 2113, 1938.

⁹ FINKELSTEIN, H. *Am. J. Dis. Child.* 54: 344, 1937.

dermatitis as an appropriate substitute. However, since the writers cannot subscribe to the concept of atopy, for reasons given elsewhere in this book, the simple descriptive term infantile dermatitis is employed. Cooke⁸² agrees in principle in the words, "And particularly is the term 'atopic dermatitis' inappropriate as it has come to imply that skin testing for immediate wheal reactions is a diagnostic procedure in eczema of the infantile type, which . . . it is not."

Together with all these authors, we differentiate between infantile and seborrheic dermatitis, although it must be admitted (see below) that it is often extraordinarily difficult, and sometimes downright impossible, to distinguish the one from the other clinically. Nevertheless, for therapeutic reasons, every effort should be made to do so in each case.

SYMPTOMATOLOGY

Infantile dermatitis is characterized by poorly defined areas of acute, subacute, or chronic inflammation of the skin, consisting of erythematous papulovesicular primary lesions, with intense itching. In the majority of cases, infantile dermatitis ends in a spontaneous cure when the child reaches the age of about 2 years; it may recur now and then, usually much later in life, in the form of some type of dermatitis. Many of these patients may sooner or later present other allergic manifestations, particularly asthma. The frequency with which this happens is indicated by the observations of Clein,²¹⁹⁸ who found dermatitis by far the most common initial allergic symptom in infants; of these cases, when followed for 10 years or more, about two-thirds had developed allergic rhinopathy, one-third pollen hay fever, and more than one-fourth asthma. None failed to develop one or more major allergic conditions during the period of observation.

In a small minority of cases the cutaneous manifestations continue throughout childhood and even into adult life, though they gradually assume a different character, presenting the typical picture of localized or disseminated neurodermatitis. This is observed not only in children in whom the skin disease has been accompanied by asthma from earliest youth, but also in other unusually severe and refractory cases. While infantile dermatitis occurs

chiefly in the so-called exudative type (Fig. 325), it is occasionally also seen in overfed and atrophic children (Figs. 326, 327). As a rule, the skin of infants of the first type is not firm and taut as is usual in overfed children, but flabby and flaccid in appearance and on touch. Adolf Czerny assumed that the condition is due to a metabolic disturbance, for which he coined the designation "exudative diathesis." When dressed or when covered up in bed, these children give an initial impression of being fat and literally overfed; undressed, however, they typically present strikingly thin thighs and calves.

The characteristic primary lesion is a small exudative papule, which may become a vesicle or be topped with a crust if the overlying epidermis is removed by scratching. The clinical manifestations begin with symmetric eczematous lesions on both cheeks—the so-called milk crusts (Fig. 328), this phase is replaced in turn by a very intensely pruritic, usually excoriated and crusted vesiculation on an acutely inflamed base (Fig. 329). These exudative lesions obviously offer terrain highly suitable for bacterial growth, and in fact very frequently lead to a secondary pyogenic infection, with general lymphadenopathy (Fig. 330). But even at this time the patient usually presents the characteristic pallor of the face. Superimposed infection with hemolytic streptococci was found by Boisvert and Powers²⁷⁰³ to originate most frequently from nasopharyngitis due to this organism, and to account for lack of therapeutic response of the dermatitis and pronounced weeping of the skin. It requires appropriate treatment, in addition to that directed against the underlying dermatitis. Other but rare streptococcal complications include bacteremia, erysipelas, progressive lymphadenopathy, and localized involvement of some internal organ, including otitis media.

The papulovesicular eruption tends to spread after a while to other parts of the body, chiefly to the forearms, and the outer aspects of the lower parts of the legs (Fig. 331). Not infrequently, other areas may also be extensively involved. The clinical manifestations are manifold: erythema, papules, vesicles,

²⁷⁰³ BOISVERT, P. L., and POWERS, G. F. *Yale J Biol & Med* 16: 593, 1934

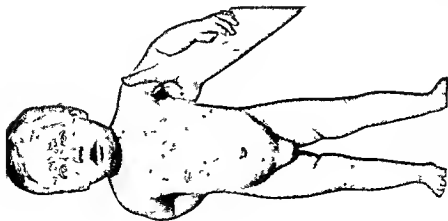


FIG 325 Latent diathesis (Czerny). Note difference between vasty face and relatively thin legs

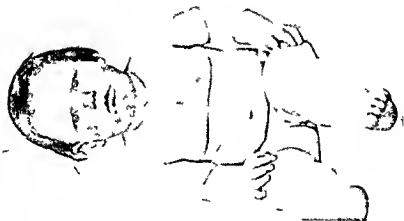


FIG 326 Overt type



FIG 327 Atrophic under type

THE THREE CONSTITUTIONAL TYPES OF CHILDREN WITH INFANTILE DERMATITIS



FIG. 328 INFANTILE DERMATITIS, DRY FORM "MILIA CRUST"



FIG. 329 INFANTILE DERMATITIS EXUDATIVE FORM



FIG. 330 INFANTILE DERMATITIS SECONDARY INFECTED FORM



FIG. 331 INFANTILE DERMATITIS INVOLVING THIGHS AND LEGS IN ADDITION TO FACE AND NECK

crusts, scales, and even wheals may exist side by side

The nature and frequency of complications appearing in the course of infantile dermatitis, including the so called "sudden death," generalized vaccinia ("eczema vaccinatum"), Kaposi's varicelliform eruption, respiratory infections, and gastro intestinal disturbances were recently reviewed by Epstein²⁵¹² and Glaser²⁷¹⁰

PATHOGENESIS

It is surely safe to say that today there is no doubt that infantile dermatitis is the expression of an allergic reaction of the body. The only controversial question is as to the extent to which foods, inhalants, contactants and endogenous allergens (metabolic products, faulty intestinal flora, bacteria from focal infection) are responsible in a given case, and as to the means by which the nature of the causal agent can best be determined.

Although there is a definite tendency at present to minimize the significance of foods in the causation of infantile dermatitis (according to Osborne et al²⁶¹⁷ nutritive allergens account for only 10 to 15 per cent of cases), numerous instances have been reported in which elimination and trial diets conclusively demonstrated that a food—most commonly wheat, milk, egg, orange, tomato, spinach, peas, or cod liver oil—was the sole cause of the condition (Schloss, Blackfan, Ramirez, O'Keefe and Rackemann, Woringer, Clem, and others). It is not unlikely that the present trend of starting various new solid foods in the first few months of infancy may constitute a predisposing factor to sensitization. It is preferable, particularly in children with positive family histories of allergy, to introduce new foods gradually and to increase the quantities slowly as tolerance for them is demonstrated. Hill and Pratt²⁷¹¹ stress the fact that milk is to be regarded as two foods, rather than one: the hypersensitivity may be related to the lactalbumin or to the casein. Occasionally, the physician will have to pay attention to the foods eaten by the mother

and possibly reaching the child by way of the breast milk (O'Keefe and Scott Shannon, Ratner, Balyeat). Thus Bulkley²⁷¹² described repeated instances of nursing infants with severe dermatitis which had long resisted energetic treatment, but which cleared after the mothers stopped drinking tea. That the foreign substance in human milk need not always be a food was shown by the case reported by Campbell²⁷¹³, the newborn infant of a doctor's wife developed such severe dermatitis each time his mother received an injection for hay fever that the treatment had to be stopped. Consideration must also be given to the fact that unaltered undigested proteins, such as wheat, alfalfa, flaxseed, cottonseed, and peanuts, sometimes pass intact into cow's milk (Sterling and Fishman,²⁷¹⁴ Rockwell²⁷¹⁵). In these cases the clinical symptoms are due not to sensitivity to milk, but to the unaltered extraneous protein contained in it.

Horesh²⁵¹³ pointed out that the odors or vapors of offending foods may suffice to produce exacerbations of infantile dermatitis, although probably not to cause the initial sensitization. In 8 cases the dermatosis which had been controlled by elimination diet was again induced by the odors of frying pork, bacon, or fish, of cooking cabbage, or of the opening of eggs. In one case, a flare of the dermatitis occurred whenever a freshly dressed chicken was brought into the presence of the patient. Two cases due to the odor emanating from eggs, reported by Oliver,²⁷¹⁶ were completely relieved of their dermatitis when eggs were removed from the house. It is obviously advisable to keep children with infantile dermatitis out of the kitchen when food is being prepared.

Most of the authorities who hold that hypersensitivity to foods is the cause of infantile dermatitis, consider only food proteins. However, there are a few who implicate animal fat. Gartye,²⁷¹⁷ for one, blames milk fat, as well as cod liver oil, and claims, furthermore, that these fat hypersensitive dermatitic children usually manifest not the exudative but

²⁷¹² BULKLEY L. D. Diet and Hygiene in Diseases of the Skin. London: Baillière Tinsdale and Cox 1913

²⁷¹³ CAMPBELL G. A. *Canad. M. A. J.* 52: 280 1945

²⁷¹⁴ STERLING A. and FISHMAN A. E. *Arch. Pediat.* 55: 172 1938

²⁷¹⁵ ROCKWELL C. E. *J. Allergy* 13: 404 1942

²⁷¹⁶ OLIVER E. A. *dis. caus. on* to Templeton 1917

²⁷¹⁷ CARTYE E. *Monatsschr. f. Kinderh.* 26: 57 1923

²⁵¹⁰ EPSTEIN S. *J. Pediat.* 26: 541 1940

²⁷¹⁰ GLASER J. *Ann. Allergy* 3: 373 1945

²⁷¹¹ HILL L. W. and PRATT H. N. *J. Allergy* 12: 113 1941

the dry condition so characteristic of seborrheic dermatitis. Because of this assumed allergy to fat, Monrad, Marfan, Gerstley, and others recommended giving children skimmed milk or butter-milk instead of mother's or cow's milk. In the case of a nursing infant it is sometimes possible, as claimed by Marfan and Turquet, to reduce the fat content of the mother's milk by placing her on an appropriate diet (limited quantities of fat and meat, no alcohol), thus bringing the milk within the infant's limit of tolerance. Leiner as well as Pulay observed cases of infantile dermatitis in which hypersensitivity to sugar could be demonstrated. As to the identification of the causative nutritive allergen, Hill and Sulzberger,²⁸⁴ Osborne and Walker,¹²⁹ Finkelstein,²⁷⁰⁷ Birt,²⁷¹⁸ and the senior author²¹⁹ have long been of the opinion that positive skin tests with food proteins, as well as the passive transfer test and the complement fixation reaction, are undependable and often actually misleading, and that only the elimination diet or, as we have shown, the propeptan method is really useful for this purpose.

Although it is true that the majority of all children suffering from infantile dermatitis give a positive reaction to raw egg white, strict elimination of eggs from the diet rarely results in an improvement of the cutaneous condition. Thus, each of 46 cases studied by Ditzkowsky et al.²⁷¹⁹ reacted on skin testing to one or more fractions of egg white, but in only 6 subjects in the entire group was clinical sensitivity to this substance noted. Moreover, the skins of these children also react to other kinds of eggs not commonly used for human consumption, such as pigeon, ostrich, gull, or lapwing eggs. Positive tests with egg white, milk, or other foods do not, therefore, permit the conclusion that a given case of infantile dermatitis is necessarily caused by these substances. Such reactions may indicate nothing more than that the skin has acquired—either during the first weeks or months of life, or perhaps prenatally—a hypersensitivity to these proteins. This allergic state can pave the way for other hypersensitivities, mediated by ingestants, inhalants, or

contactants. This concept of a metallergic mechanism in infantile dermatitis would seem to be supported by the following clinical observations. Frequently after an infectious disease or an exacerbation of one (e.g., tonsillitis, otitis, bronchitis), and occasionally following vaccination or gastro-intestinal disturbances, there is a flare at the sites of former skin manifestations, and surprising therapeutic results are sometimes achieved by eradication of the foci of infection. On the other hand, the elimination of a great variety of nonspecific external irritants (water, heat, sunlight, friction) often has a decidedly beneficial effect. Hill and Sulzberger²⁸⁴ venture the opinion that the mechanism in infantile dermatitis is a heterophile one, and that the dermatitis may be due, for example, not to egg, but to allergens immunologically related to egg.

However, intracutaneous or subcutaneous administration of extracts of egg white, milk, or wheat occasionally produces severe anaphylaxis, without causing a flare of the cutaneous manifestations. In instances of this kind, the hypersensitivity to egg as demonstrated by the skin test, while specific, is not the underlying cause of the dermatitis. Moreover, the feeding of a new protein to an infant—for example, soy bean protein—is followed for a short time by the development of antibodies, as demonstrated by a positive intracutaneous test (Hill¹²⁹). Elimination or addition of these proteins to the diet will neither improve nor aggravate the condition. Hill therefore interprets the temporary reactivity to such foods as an expression of a nonetiological naturally produced hypersensitivity.

Finally, it should be pointed out that the reaction to egg white is of no value as a means of clinical differentiation of the various forms of dermatitis in children. While in the exudative type there is a positive test in the great majority of instances (in 85 per cent of cases, according to Sulzberger and Hill, and Ditzkowsky et al.; in 82 per cent, Moro; in 69.5 per cent, Strobl and Wasitzky, in 65 per cent, Urbach; in 54 per cent, Woringer; in 50 per cent, Rosenbaum), patients with seborrheic dermatitis not infrequently react in the same manner (Urbach, Miyasaki, Minami); indeed, some children with the latter condition react

* BIRT, A. R. *Canad. M. A. J.* 43: 520, 1940.

²⁷ DITZKOWSKY, S. E., HICHT, R., COLE, A. G., and LEVIN, B. *Arch. Dermat. & Syph.* 48: 2-8, 1943.

other skin diseases (Simon^{26,28}). Sulzberger and Baer⁷² point out that human dander consists largely of five elements, each of which is in turn a composite of many ingredients: desquamated horny epithelium, sebum, sweat, micro-organisms, and collected dusts and other extraneous matter.

DIAGNOSIS

The differentiation between seborrheic dermatitis and infantile dermatitis is often very difficult to establish. However, in patients of this age, seborrheic dermatitis is likely to begin with intertrigo in the groins, axillae, and other folds. Furthermore, a blepharitis is very

other hand, seborrheic manifestations so frequently precede the development of infantile dermatitis, and mixed forms are so common, that there is evidently some relationship between the two (Hill^{77,78}). Finally, the senior writer¹⁰ has observed a number of cases of seborrheic dermatitis gradually changing into neurodermatitis (FIG. 333).

Infantile dermatitis, on the other hand, is characterized by intense itching, exudation, crust formation, and secondary infection, furthermore, the skin folds are not involved, and there is no blepharitis.

As to the methods of determining the causative allergen, the reader is referred to the sec-

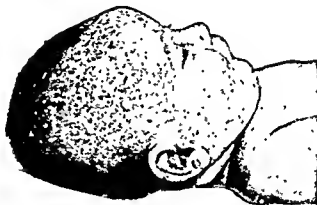


FIG 332 SEBORRHEIC DERMATITIS LIMITED TO SCALP "CRADLE CAP"

commonly present. Another characteristic symptom is the greasy scaling of the scalp ("cradle cap," FIG. 332), which may extend to other parts of the body, usually to the face, neck, shoulders, and trunk, forming large irregularly configured areas by fusion. The eruption is essentially a dry scaly one, usually with rather sharply defined margins, and of a yellowish-pink color. The patches do not ooze unless they are rubbed. In severe cases, an erythroderma may develop, its severest expression being Leiner's disease (erythroderma desquamativa). The characteristic primary lesion is a red scaly papule, which later is transformed into a greasy scaly crust.

There is no evidence to indicate that seborrheic dermatitis is of allergic origin. On the

tion on pathogenesis, where the pitfalls of skin testing and the merits of elimination and environmental tests are fully discussed. The illuminating results of the investigations by Wilmer and his associates, among others, merit special mention: of 44 infants who repeatedly had positive reactions to milk and/or egg, definitely allergic symptoms were evidenced by only 12. Furthermore, the advice of Hill^{77,78} may be appended here, to the effect that if skin testing is undertaken, it should be done by the scratch and not by the intracutaneous method, since even normal infants may give a positive intracutaneous reaction

for a short period after eating a food for the first time

THERAPY

The first step in management is the elimination of all sources of local irritation and of all known factors of contact allergy. Since many of the agents act as inhalants as well as contactants, removal of them will also be of benefit in the large group of cases of infantile derma-

and rugs and (b) chemical substances including floor wax and insect sprays, medications, cosmetics of the parents and lacquered toys. It is well to use soft well washed unstarched linen or cotton garments. Mattresses, pillows and blankets should be enclosed in allergen proof covers. Great care must also be taken to ensure that no soap or laundry chemicals remain in the clothing or bed linen. Thorough and repeated rinsing of all garments and linens is necessary. Quite frequently the success or failure of these measures hinges on a personal examination of the child's environment by the physician. Information given by the mother or nurse cannot entirely be depended upon.

If this regimen combined with local treatment (see below) does not bring about improvement within two weeks, elimination diets should be instituted (Fros 334-335). These are not only indispensable in treatment but constitute a therapeutic test that for the reasons previously given is superior to skin testing. They can be of value only if strictly adhered to. Elimination diets for the nursing mother frequently produce favorable results in the dermatitic nursing. Needless to say it is not easy to discover the identity of the allergenic food in the mother's diet. It is said that it is often one for which she had a craving during pregnancy. In the case of milk fed babies a first trial with evaporated or superheated milk (kept at a temperature of 240°F for one half to one hour) may be made since as Ratner and Gruehl²² have shown heated milk has reduced anaphylactogenic properties. However if this approach fails the substitution of goat's milk is sometimes successful. It is advisable to feed each different milk for from five to seven days, since it often requires at least that length of time for any appreciable clinical change to become evident.

If no animal milk can be tolerated a soy bean preparation should be tried (Hill and Stuart^{27, 28}). There are a number of different preparations on the market the most popular being Sobee (Mead Johnson and Company) and Mull Soy (Borden Company). While these fulfill the nutritional requirements of



FIG. 333 SEBORRHEIC DERMATITIS CHANGING INTO NECRODERMATITIS

titis due to inhalant allergy. It is absolutely essential to convince mothers and nurses that their full cooperation is a paramount factor in obtaining satisfactory results.

The child should be placed in a dustproofed room and should be kept away from (a) such environmental allergens as wool (in clothing and blankets), silk, feathers (in pillows, quilts) and other animal epidermal substances including dander of pets, as well as house dust

²² RATNER, B. and GRUEHL, H. L. *Am. J. Dis. Child.* 49: 267, 1933.

^{27, 28} HILL, L. W. and STUART, H. C. *J. A. M. A.* 93: 98, 1929; 11: 1, L. W. *Am. J. Dis. Child.* 41: 733, 1911.

the growing infant, they may cause diarrhea and vomiting. According to Levin,⁷²⁶ Kreime O'Soy (Madison Foods, Madison College, Tenn.) is, as a rule, better tolerated. It contains 2.28 per cent of protein (from soy bean), 5.22 per cent of fat (soy bean oil), and 4.45 per cent of carbohydrate (from soy bean and added dextrose). Soyola (Wyeth) is also available. The diet consists of the soy bean emulsion diluted with water in the same proportion as that in which cow's milk would be diluted. Additional carbohydrate in the form

Vitamins must be given, depending on the infant's requirements, the synthetic preparations being preferable in order to avoid the possibility of allergy to protein in the sources from which the natural vitamins are derived, such as cod liver oil, liver, or yeast. Suitable synthetic vitamins include provitamin A (Carotene or Caritol, 8 to 10 drops), thiamin hydrochloride (0.25 mg.), riboflavin (0.5 mg.), niacin amide (4 mg.), ascorbic acid (50 mg.), and vitamin D (viosterol or Drisdol, 8 to 10 drops, once a day).



EFFECT OF ELIMINATION DIET ON INFANTILE DERMATITIS

FIG. 334 Appearance before treatment

FIG. 335 After fourteen days of diet free of animal protein.

of cane sugar is added in quantities of 2 to 4 tablespoonfuls for the twenty-four-hour formula. For infants over 5 months of age, sobee is added to the diet as a cooked cereal. It should be cooked for about one hour until it is quite thick and firm. Stoesser⁷²⁷ not only confirmed the value of soy-bean feeding in milk-sensitive and multiple-food-sensitive infants, but also found in some instances that its use for some weeks led to tolerance of other foods to which they had previously demonstrated clinical sensitivity.

Since quite a few children develop hypersensitivity to soy bean preparations, it is essential to have available milk substitutes derived from cereals, vegetables, or meats. Wolfe and Silverstone⁷²⁸ devised nine such substitutes prepared from oats, barley, lima beans, peas, taro, rice, rye, and corn flour with the addition of oil (cottonseed, olive, sesame, corn, and peanut), gelatin, dextrose, imitation vanilla, salt, crushed bone phosphate or calcium phosphate, ferric chloride, and sometimes saccharine. According to

⁷²⁶ LEVIN, S. J. *J. Pediat.* 17: 79, 1940

⁷²⁷ STOEßER, A. V. *Ann. Allergy* 2, 403, 1944

⁷²⁸ WOLFE, I. Z., and SILVERSTONE, P. C. *J. Pediat.* 21: 635, 1942

Feingold²⁷²⁹ another vegetable substitute for milk is taro a plant commonly eaten in Hawaii in the form of a mush known as poi. As an alternative to soybean milk Stuart²⁷³⁰ described a strained meat formula which can be readily prepared in the home. Glaser²⁷³¹ states that specially strained (homogenized) meats beef lamb beef liver with added ingredients following a suggestion of Rowe's should soon be commercially available as milk substitutes.

Protein hydrolysates may be employed as a source of nitrogen in allergic infants and children. Since the various proteins are composed of essentially the same amino acids the process

noted improvement in highly allergic patients fed a mixture of 70 Gm of amino acids 140 Gm of oil 250 Gm of dextrose 20 Gm of salt mixture and synthetic vitamins. Since this synthetic diet has an unpleasant taste feedings were administered by stomach tube at intervals of two to four hours.

The present writers have used Aminoids (Arlington) Amigen (Mead Johnson) and Parname (Stearns) in children allergic to milk. While the results were often satisfactory in some infants the hypersensitiveness was so extreme that they reacted to these digests which it must be remembered contain traces of their higher protein constituents.



EFFECT OF DIET IN CASE OF INFANTILE DERMATITIS DUE TO MILK AND MILK PRODUCTS

FIG. 336 Appearance on admission to hospital



FIG. 337 After twenty-one days on soybean diet

of artificial digestion can be carried to the point where individual specificity of structure is lost. Hill⁶¹⁸ reported that 36 dermatitic infants allergic to milk tolerated such a preparation perfectly. The mixture which was given for as long as three months contained 20 per cent protein hydrolysate. Definite improvement in the dermatitis and satisfactory weight gain were observed in 19 of these infants. By a similar method Beling and Lee⁷³ cured a milk allergic child with an erythematous rash and generalized nutritional edema in fifteen days. Olmsted and his co-workers⁷³⁹

The effects of the diet should become apparent within a week (Figs 336-337). After the condition has healed or materially improved the following foods may be added one at a time at three day intervals according to the infants age desire and digestive and allergic tolerance: corn meal rice oatmeal barley flour tapioca carrots lettuce asparagus applesauce bananas and bread. Reactions should be carefully noted. If the condition flares up after a certain food has been added to the diet this item should be withheld until the eruption has disappeared. Milk eggs tomatoes and oranges are the last foods to be tried on the baby.

For the purpose of this regimen a food diary is of particular help. It consists of a

²⁷²⁹ FEINGOLD B. F. *J. Allergy* 13: 488, 1942.

²⁷³⁰ STUART G. J. *ibid.* 16: 23, 1945.

²⁷³¹ GLASER J. *ibid.* 15: 283, 1944.

⁷³ BELING C. A. and LEE R. E. *Arch. Surg.* 43: 35, 1941.

complete, carefully kept record, with notations of the time of ingestion of each food—including such overlooked items as sweets—on the left-hand page, and of fluctuations in the symptomatology in some detail on the right-hand page

When injected protein, whether in milk or other food, has been shown to be the cause of an infantile dermatitis, a properly pursued course of specific propeptan therapy (see p 220) is of great value and frequently results in tolerance for normal amounts of the responsible food without consequent cutaneous inflammation.

broth and even small amounts of meat may be tried

Undernutrition, diarrhea, and infection, if present, must all be cleared up in the exudative as well as in the seborrheic type of dermatitis in children. The writers have quite frequently observed an onset of skin manifestations in infants after prolonged diarrhea. It seems likely that the intestinal allergization was initiated by the diarrhea. Furthermore, we have repeatedly noted that local infections, such as tonsillitis, otitis, bronchitis, and pyelitis, as well as those in the intestines, may produce a rather severe flare of the skin disease



EFFECT OF DIET IN CASE OF INFANTILE DERMATITIS DUE TO ANIMAL AND VEGETABLE FAT

FIG 338. Appearance on admission to hospital.



FIG 339. After twelve days of fat free diet

For cases presenting a predominantly seborrheic type of dermatitis, Finkelstein²⁷⁷ recommends a diet poor in fat and sodium chloride but relatively rich in protein and high in fruit and vegetables. This means that milk, as well as any other food containing animal or vegetable fat, is excluded (Figs 338, 339). On the other hand, 2 or 3 teaspoonfuls of amino acids should be given daily for about four weeks. However, children are not infrequently allergic to these products, as has been seen by the authors. There should also be sufficient vitamin B in the diet. After the condition has begun to improve, either buttermilk or cottage cheese is added; later beef

In addition to the general and dietary management, external local treatment is indispensable, though it is in itself merely palliative, not curative. To begin with, bathing is strictly forbidden, and only the uninvolved skin areas may be washed with soap and water. The skin may be cleansed with plain petrolatum, mineral oil, olive oil, or preferably by means of compresses. In order to prevent scratching of the lesions and avert the consequent danger of secondary infection, the arms and legs should be restrained by tying them to the sides of the bed. In milder cases, the arms may be splinted with stiff cardboard cuffs, covered with cotton and reaching well above

the elbows (FIG 340) The fingernails should be kept closely trimmed

When the condition is severe it is advisable to have the infant rest on a large piece of celluloid (a cleansed roentgen film) in order to prevent rubbing on the bed sheets Sedation will often be found necessary In some instances it will be found expedient to hospitalize the child in which event every precaution must be taken to prevent cross infection since it is a known fact that such patients are particularly prone to acquire otitis media bronchopneumonia and similar infections

acid solution 1 10 000 acriflavine solution diluted Burow's solution or potassium permanganate in a 1 6 000 dilution these are applied to the most severely affected areas three times daily for one hour and changed every ten minutes In severe cases it will be necessary to cover the face with a mask of linen coated with a thick layer of boric acid ointment (U S P IX—without wax) and to apply the compresses over the mask In the event of secondary infection a 5 per cent sulfathiazole cream or penicillin ointment may be used instead When there is no more

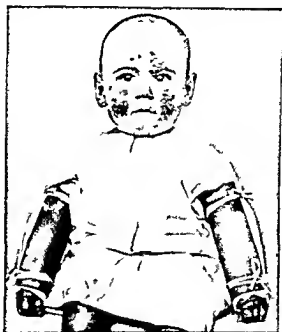


FIG 340 METHOD OF RESTRAINING INFANTILE DERMATITIS PATIENT FROM SCRATCHING

Control of pruritus by means of large doses of thiamin chloride was reported by Shannon²⁷³³ While vitamin B complex is considered a useful adjunct in the treatment of infantile dermatitis by Harris and Gay²⁷³⁴ and Epstein²⁶¹⁹ Sulzberger and Baer²⁷³⁵ were unimpressed with the results obtained with various vitamins including vitamin B complex

In acute cases the condition can be relieved by wet dressings of 2 per cent boric

crusting or infection the wet dressings may be placed directly on the face and the following lotions may be thinly and gently applied in the intervals between the wet dressings

	Gm or Cc	
℞ Olive oil		
Zinc oxide		
Talc	aa 15 0	aa 3iv
Glycerin		
Water	aa q s ad 90 0	aa q s ad f3i
℞ Bismuth subgallate		
Zinc oxide		
Talc	aa 15 0	aa 3iv
Cottonseed oil		
Glycerin		
Water	aa q s ad 120 0	aa q s ad f3iv

²⁷³³ SHANNON W R U o & Cutan Rev 46 786 1942

²⁷³⁴ HARRIS A and GAY L N J Allergy 14 335 1943

²⁷³⁵ SULZBERGER M B and BAER R 1943 N bk Dermat & Syph Chicago Y bk Pub 1944

When the acute dermatitis has subsided, crude coal tar, beginning with 0.25 per cent and slowly increasing to 5 per cent, is extremely valuable if well tolerated. For the first two days the tar ointment should be applied to a limited area, in order to determine whether or not it irritates the skin.

	Gm or Cc.	
R Crude coal tar	0.6-6.0	gr x-5iss
Olive oil	20.0	5v
Zinc paste	q s ad 120.0	q s ad 3iv
	Gm	
R Naftex (Lascoff)	6.0-30.0	5iss-3i
Zinc paste	q s ad 60.0	q s ad 3u

In severe cases, small fractional doses of X ray are sometimes of value.

The seborrheic state of the scalp may be treated with a sulfur cold cream.

	Gm or Cc	
R Precipitated sulfur	1.2-2.4	gr xviii-xxxvi
Boric acid, 1 per cent solution		
Anhydrous lanolin	24.45.0	24 3iss
Petrolatum	q s ad 120.0	q s ad 3iv

6. SEBORRHEIC DERMATITIS

On clinical grounds, Unna segregated from the dermatitis group certain cutaneous manifestations that are commonly encountered in the so-called seborrheic regions and called them "seborrheic eczema." Since they are almost never expressions of an allergy they need no further discussion here. Differentiation between this condition and infantile dermatitis is important for therapy and was therefore discussed there in some detail.

7. INFECTIOUS AND PARASITIC DERMATITIS

This group includes a number of subdivisions, which are characterized clinically in most instances by rather sharply defined pityriasisform or psoriasisform eruptions appearing in the sites of predilection (axilla, groin, scalp, over the sternum), and pathologically by their bacterial, fungous, or other micro-organismal origin. All are amenable to cure by the indicated antibacterial or antiparasitic therapy. Darier²⁷³⁶ and Miescher²⁷³⁷ have described this group under the heading of

"eczematids," to connote the clinical relationship to eczema, and at the same time to indicate the unrelated etiology. Seborrheic dermatitis, which responds so well to sulfur, is now also regarded by some authorities as an infectious epidermitis—as are also, of course, the strepto- and staphylococcal, for which penicillin ointment (500 Oxford units per cc), 5 per cent sulfathiazole cream, and 1:10,000 acriflavine cannot be too highly recommended. Also to be included here are certain forms of trichophytosis, epidermophytosis, and moniliasis that respond to antiparasitic treatment.

The etiologic investigation of these cases is handicapped. The mere isolation of streptococci, or *Staphylococcus aureus*, or monilia, for example, from the dermatitic lesions, is often misleading, since most of the microbic dermatitides are caused by micro-organisms which may be found on any skin. Moreover, dermatitis of other origin frequently becomes secondarily infected with pyogenic bacteria or fungi, although these are without primary etiologic significance. On the other hand, the absence of bacteria or fungi does not disprove the microbic origin, as we may be dealing with an allergic "id" lesion. Tests for skin sensitivity to bacterial vaccines or extracts are only of limited value. It has been previously mentioned that microbic allergens are capable of eliciting three types of cutaneous reactions: (1) delayed, tuberculin- or trichophytin-type; (2) immediate whealing type, which is relatively common with molds and monilia, rather rare with bacteria and trichophytin; and (3) eczematous type of reaction (epidermal-contact type), which may play a rôle with trichophytin or oidiomycin in dermatitis. In microbic dermatitis, all three forms of sensitivity can be observed. The ubiquity of both staphylococci and streptococci explains why the great majority of persons react to their extracts. A clue is obtained, however, if there are marked local reactions, and especially if they are combined with a focal flare of the original lesions. Antibacterial and antiparasitic therapy will cure only those cases in which the micro-organism is the primary cause of the condition.

According to Epstein,²⁸¹² infectious dermatitides appear clinically under a great variety of pictures. Not all of them are characterized by

²⁷³⁶ DARIER, J. *Précis de dermatologie*. Paris: Masson, 1928.

²⁷³⁷ MIESCHER, G. *Dermat. Wchnschr.* 101: 1195, 1935.

sharply outlined pityriasisform or psoriasisform lesions. Numerous infectious dermatitides present just the ordinary morphology of dermatitis and are frequently confused with it.

Bacterial dermatitis is called infectious eczematoid dermatitis by most physicians. This term is used to designate dermatitis that, by reason of the presence of pustules or its sharp outlines or association with other foci, suggests a parasitic origin. It apparently covers both dermatitides of primary microbic etiology and those of other origin which have become secondarily infected. Elimination of the focus of infection is of primary importance. Vaccines have been found useful by some and worthless by others. Epstein⁷⁶¹ advocates that it be given a trial in stubborn cases. The sulfonamides and penicillin mark a great advance in treatment.

Infectious eczematoid dermatitis frequently becomes complicated by epidermal contact type sensitivities, particularly to medication used locally. Moreover, these patients apparently have a greater capacity to develop drug sensitivities to internally administered drugs. This has become especially manifest, as Epstein points out, since the widespread use of sulfonamides in microbic dermatitis. Thus in cases of severe sensitization from topical application of sulfonamides as reported by Livingood and Pillsbury¹⁵⁹ and Shaffer et al.,¹⁶⁰ the pyogenic infection, primary or secondary, plays a definite part.

Haxthausen²⁷³⁸ offered the hypothesis that the micro organisms of the skin may be operative in the pathogenesis of certain allergic cutaneous eruptions inasmuch as they represent the foreign protein which, in combination with substances applied to the skin, results in the formation of complete antigens capable of producing antibodies that are reactive with the simple compounds as well. The nature of the protein, too, undoubtedly is significant since it is known from other experimental work that some micro organisms exert a more marked activating effect upon haptens than do others.

The demonstration of pathogenic fungi, such as *Trichophyton* or *Monilia albicans* establishes the diagnosis of parasitic dermatitis

although the fungi may be secondary invaders. Negative findings both microscopically and by culture are so common especially in fungous infection with allergic manifestations that they do not exclude the diagnosis. Tests for skin sensitivity to fungous extracts are only of limited value. In Epstein's⁷⁶¹² opinion however both the trichophytin and oidiomycin tests are not as useless as is generally assumed. In cases of dermatitis due to fungus sensitization, these tests may produce a different picture from the ordinary tuberculin or trichophytin type of reaction. Instead of reaching a maximum after forty eight hours and then fading, the reaction may change gradually from this form into an eczematoid lesion, frequently producing a picture identical with that of the dermatitis. This form of reaction seems rather good evidence particularly if it can be repeated with the same results.

Parasitic dermatitis frequently becomes complicated by epidermal contact type sensitivities. Perhaps the best known example of such an interplay between parasitic and epidermal sensitivity is the fact that patients with an epidermophytid of their hands are very prone to develop epidermal (contact type) sensitivities—for example, to soap or rubber gloves. The interrelationship of dermatitis from cutting oils and latent "ids" was stressed by Biram.²⁷³⁹

Another subdivision is so called dyshidrotic dermatitis or cheiropompholyx, which is partly of mycotic origin but may be maintained, to some extent, by hematogenous infection from some focus, or may constitute a manifestation of contact allergy (Avit-Scott,²⁷⁴⁰ Goodman²⁷⁴¹), food allergy, or even drug allergy (Schuermann²⁷⁴²).

Because of the practical importance of recurrent vesiculopustular eruptions of the hands (Fig. 341) and feet both for differential diagnosis and therapy we should like to append a very useful grouping contributed by Carpenter.²⁷⁴³ These conditions may be conveniently divided according to etiology into

(I) *Ingestion Group*—Lesions that are actually produced or aggravated by the ingestion of foods or drugs

²⁷³⁸ HAXTHAUSEN J R. *Indust Med* 12: 204 1943

²⁷³⁹ AVIT-SCOTT J. *Brit J Dermat* 46: 378 1954

²⁷⁴⁰ GOODMAN H. *Acta dermat venerol* 13: 25 1954

²⁷⁴¹ SCHUEMMER H. *Dermat Wchnschr* 196: 461 1958

²⁷⁴² CARPENTER C C. *J M Soc New Jersey* 42: 262 1945

(McLachlon and Brown^{2,14} Wise^{2,15}) Although any food may be suspected it seems that the citrus fruits are the ones most frequently the culprits. Among the drugs that have been incriminated by various authors are the salicylates, ephedrine, mecholol, sulfonamides, and penicillin (for literature see Carpenter^{2,16}).

(2) *Contact Group*—As reactions to local applications of antiseptics, irritants, or medications, or by various occupational causes. This is particularly true of housewives, doctors, nurses, and dentists from the use of strong soap solutions, bleaches, and disinfectants, or as the result of working in rubber processing, leather work, photography, etc. Patch tests with all suspected agents should be carried out.

(3) *Fungus Group*—A direct infection of the feet or hands by fungi or yeast, or an allergic manifestation of

either a direct infection of the skin at some remote area or by internal foci of infection.

(5) *Miscellaneous Group*—These include those due to gastro-intestinal intoxication, changes in temperature and climate, nervousness, or idiopathic causes.

This subdivision and appropriate etiologic therapy will facilitate management of these often recalcitrant vesicular eruptions.

From these many examples it will be seen that the treatment of dermatitis cannot be based upon the clinical picture alone, but also requires thorough allergic, bacteriologic, and chemical study.



FIG. 341. CHRONIC DERMATITIS OF THE HANDS OF BACTERIAL ORIGIN.

the skin of the feet, hands, or both to a primary fungus or yeast focus elsewhere on the skin, in the gastro-intestinal tract, or in the vagina. Such eruptions are referred to as "ids." The diagnosis of a primary fungus or yeast infection of the hands and/or feet or of intertriginous spaces with a secondary eruption of the hands and/or feet rests on the microscopic or cultural demonstration of a fungus or yeast in the suspected primary focus and a positive trichophyton or oidiomycin test which may produce a local aggravation of any existing "id" within forty-eight hours.

(4) *Bacterial Group*—Direct infections of the hands and feet or both, with Staphylococci and Streptococci or an allergic form in which the "ids" are produced by

8. METABOLIC DERMATITIS

This term is used to embrace those cases of dermatitis that are proved to be due to faulty metabolic functioning of any of the internal organs. Of course, it is not for a moment claimed that the majority of these cases are allergic in nature. However, it is conceivable that, in particular instances, products of a pathologic intestinal flora or of an endocrine dysfunction may act as endogenous allergens. Moreover, there is some basis for the assumption that toxic substances may induce a state of hypersensitiveness that, according to our nomenclature, is pathergic in character.

Dermatitis may have its origin in dysfunction or disease of the gastrointestinal tract.

* McLACHLON, A. D., and BROWN, H. W. Brit. J. Dermat. 46: 457, 1954.

* WISE, F. discussion to Seneff, F. E. Recurring Vesicular Eruptions of Palm and Soles, Am. Acad. Dermat. Meeting, New York, 1941.

After cure of enteritis or colitis or even of constipation of the chronic type many such skin eruptions disappear completely. Not infrequently it is necessary to administer pancreatic enzymes at the same time since a hypofunction of the pancreas may also be present.

Diabetes mellitus likewise plays a significant part in the causation of eruptions of this type; this disease should be especially considered in cases with dermatitis around the body orifices (mouth, anus, urethra, vagina). Therefore the glucose tolerance test should be performed in those patients with chronic resistant eczema. Furthermore, as the senior author⁷⁷⁴⁸ pointed out, normal blood sugar curves may occasionally be misleading, and only determination of the sugar content of the skin will reveal the presence of a metabolic disturbance—the so called cutaneous diabetes.¹¹⁰⁸

The modern French school's concept of liver disease as a cause of dermatitis should also be mentioned here. The senior author has although rarely observed certain cases of severe chronic dermatitis that could be controlled only by finding and treating hepatic dysfunction (FIG. 342).

It is particularly important to recognize the relationship between ovarian disorders and dermatitis and always to keep this possibility in mind. To what extent a menstrual toxin or allergen may be involved in the etiology of a menstrual dermatitis must be determined in each case (see p. 856). By systematic intramenstrual injections of the patient's own serum one may frequently obtain highly satisfactory results in the treatment of menstrual dermatitis. It is essential that the blood be withdrawn at the time when the dermatitis flares shortly before menstruation.

Finally, there is dermatitis of local metabolic origin—for example, varicose dermatitis produced by local circulatory disturbances. In these conditions proper vascular therapy to improve the cutaneous blood supply constitutes the chief remedy.

9. DERMATID

The last form of dermatitis to require discussion here is that based on the mechanism of autosensitization as shown by Whitfield.⁴⁹⁷

Its clinical picture usually presents a generalized papulovesicular eruption following severe scratching or irritating therapy for a localized chronic dermatitis. There are good reasons to assume that this eruption is caused by hypersensitiveness to skin products that have become foreign to the body. Similar observations were reported by Brown⁵⁹⁸ Jaffrey.²⁷¹⁷



FIG. 342. DERMATITIS ASSOCIATED WITH LIVER DISEASE.

Case of 36-year-old woman suffering from generalized dermatitis for eighteen months. This was resistant to all forms of therapy until liver disease was discovered by liver function tests and treated by diet and insulin.

introduced the apt term dermatid for this phenomenon.

Closely allied to the dermatid is the keratid of Hopkins and Burky⁵⁵⁸ which they attribute to local autosensitization to the patient's own keratin (or a product of keratin) as a result of the synergistic action of staphylococcus toxin along with trauma at the site of

⁷⁷⁴⁸ URBACH, E., DEBISCH, F., and SIECH, G. *Klin. Wchnschr.* 16: 452, 1937.

²⁷¹⁷ JAFFREY, W. R. *Canad. M. A. J.* 37: 478, 1937.

the lesions. This concept is supported by the demonstration by Hecht, Sulzberger, and Weil⁵⁷ that specific (precipitin) antibodies can be produced in rabbits by sensitizing them with homologous skin extracts, provided the animals were injected with staphylococcus toxin as a synergistic agent. These authors are inclined to explain several phenomena observed in dermatitis, such as the spontaneous continuation or spread of dermatitis lesions and the so-called jumping about of dermatitis, in the following way. At the inception of the dermatosis the skin is damaged, and some of its constituents denatured; the new products are antigenic and are absorbed. Thus the individual becomes sensitized to his own skin. The result is that lesions subsequently develop at sites of trauma or inflammation due to the action of antiskin antibodies which react locally with liberated skin antigen. The "id" concept itself is more fully discussed on page 782.

C. URTICARIA

It should be stressed, in the first place, that many physicians and patients still labor under the misapprehension that all urticaria is to be regarded as allergic in origin. Because of this widespread belief, we have considered it expedient to include, in the section on etiology, not only a discussion of the various allergens commonly eliciting urticaria, but also a brief review of the many other mechanisms responsible for it. Furthermore, there are few other allergic diseases in which predisposing factors play so important a part. For this reason, they will receive due consideration along with the precipitating factors constituting the so-called trigger mechanism. In the following pages, the term urticaria will be understood to refer to either the acute or the chronic forms, but not to urticaria factitia or to lichen urticatus (papular urticaria), both of which are considered in detail later.

Urticaria is a very common disease. According to Swinny,²⁷⁴⁵ 22.3 per cent of a group of 958 persons whose personal and family histories were negative with regard to asthma and hay fever, had hives at some time in their lives. The percentage would

probably be much greater if all mild, evanescent conditions had been recalled by the patients.

In the senior author's own material,³²² consisting of 500 carefully investigated cases of urticaria, only some 15 per cent showed family histories of allergic diseases—and it must be borne in mind that not every instance of asthma, migraine, or urticaria is necessarily of allergic origin. Approximately the same percentage would have been obtained among a similar number of nonallergic patients. On the other hand, Stokes, Kulchar, and Pillsbury²¹²⁹ found a familial and hereditary urticariogenic background in 60 per cent of their cases, as compared with a figure of 25 per cent for the controls. Furthermore, the high incidence of migraine in the families of the female patients is worthy of note (Urbach³⁷²).

The personal histories in our material were of no great significance as an indication of a close relationship with other allergic diseases. However, in a group of 633 patients with asthma and hay fever, Swinny²⁷⁴⁵ found the incidence of urticaria to be two and a half times greater than in a nonallergic group. Concurrent angioneurotic edema is not infrequent, our figures of from 18 to 21 per cent coincide closely with those of Stokes, Kulchar, and Pillsbury²¹²⁹ (18 per cent). Previous attacks of urticaria were reported by men in 12 per cent and by women in 21 per cent of cases.

Urticaria occurs far more commonly in women than in men. The sex distribution in our cases—among which 39 per cent were men and 61 per cent women—corresponds to that found by Fink²⁷⁴⁹ and Stokes²¹²⁹ and their associates (31 and 33 per cent of cases male, and 69 and 66 per cent female, respectively).

Furthermore, it is interesting to note the incidence of urticaria according to age. The disease is not often observed in children under the age of 10 years, in fact, urticaria during the first year of life is considered a rarity. However, Wolff²⁷⁵⁰ reported a typical attack of hives in an infant 2 days old. About one-third of all urticaria patients are in the third decade of life and roughly one-fourth in the fourth decade. Next in order of incidence is the fifth decade (14 per cent), followed by the

²⁷⁴⁹ FINK, A. I., and GAY, L. N. *J. Allergy* 5, 615, 1934.

²⁷⁵⁰ WOLFF, S. *Arch. f. Kinderh.* 109, 89, 1936.

second and the sixth with approximately the same figure each (8 per cent). Relatively few individuals past the age of 60 years are afflicted. However the senior author has observed initial acute attacks of urticaria in a man of 71 and in a woman of 79 years.

While the average duration of urticaria under our observation was somewhere between one week and three months the course was longer in nearly half the cases specifically from four to twelve months in 19 per cent from one to five years in 20 per cent from six to ten years in 4 per cent and from eleven to twenty years in 1.5 per cent of the cases. In a few isolated instances the condition persisted for thirty, forty and even fifty years.

1 SYMPTOMATOLOGY

In the acute form of urticaria there is first some slight local discomfort soon replaced by intense itching which is followed by the sudden appearance of wheals (FIG 343). These are usually white, not always sharply defined and range from lentil to palm sized occasionally however they become confluent and thus cover large areas of the trunk or extremities. The individual hives may persist for minutes, hours and sometimes even for one or two days. Their color is not invariably white in some cases the lesions are pinkish to reddish from the outset. Moreover the clinical appearance of the urticarial exanthem is extraordinarily polymorphous in other ways. For one the urticarial component is sometimes so negligible that the eruption may present a measles like picture; however in such cases the transitory nature of the manifestations and the rapid changes from day to day leave no room for doubt as to the nature of the eruption. In still other instances the garland shaped arrangement of the lesions (FIG 344) or their polycyclic borders (FIG 345) are worthy of note—as is the erythema multiforme like appearance in another group. In addition to the urticarial exanthem generalised edema of the skin of the face and body is not infrequently observed. Occasionally the intense itching alters the clinical picture by reason of the superimposed multiple excoriations. Lastly mention should be made of the micropapular form which is characteristic of so called sweat urticaria.

Urticarial manifestations may appear not only on the skin but also on the mucosa especially that of the mouth (lips, tongue) and larynx. Occasionally the gastro intestinal and urogenital tracts are similarly involved or they may even be independently affected. Moreover albuminuria which is sometimes observed in association with urticarial eruptions and especially with serum exanthems or with angioneurotic edema is probably at



FIG 343 WHEAL FORMATION CHARACTERISTIC OF URTICARIA

tributable to a transitory serous inflammation of the urinary tract.

The main difference between the acute and the chronic forms of urticaria is to be found in their courses rather than in their respective clinical pictures. The acute type generally disappears without treatment within a matter of days or weeks. Chronic urticaria on the other hand can continue to distress the patient for months and even for years, however

even in this form of the disease, symptom-free periods of varying duration are commonly observed.

For reasons not as yet explained, urticarial eruptions, and especially the accompanying pruritus, are most severe during the night. Exceptions to this general rule are the cases that are due to exogenous agents.



FIG 344 GARLAND-SHAPED FORM OF URTICARIA, DUE TO HYPERSENSITIVENESS TO FOOD (STRAWBERRIES)

2. ETIOLOGY

The problem of the etiologic factors in urticaria is, of course, of paramount importance. In 88 per cent of the 500 cases investigated, we were able to determine the cause either definitely or at least with considerable probability. We based our diagnoses upon avoidance and exposure tests, not upon skin tests. Before discussing the detailed causes classified in Table 60, it must be pointed out that no more than 117 cases (less than one-fourth of the total) were definitely found to be of allergic origin, if the term allergy is understood to apply only to those hypersensitivities

that are based on a proved antigen-antibody reaction. In 4.6 per cent of the cases we were unable to confirm, but had valid reasons for assuming, the presence of endogenous allergy. The largest group, comprising 308 cases (62 per cent), showed the most varied causative factors, as shown in Table 60. Since it was not possible to establish the fact of an allergic mechanism in any of these

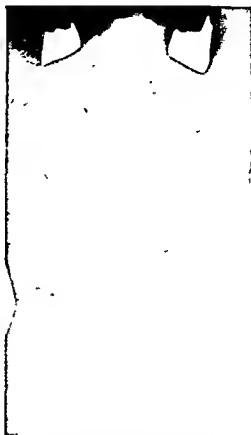


FIG 345 POLYCYCLIC FORM OF URTICARIA, DUE TO BACTERIAL ALLERGY (TONSILLITIS)

cases, they are classified as pathergic. In the remaining 52 cases, it was impossible to establish any etiologic factor, and they are listed as of unknown etiology.

Fink and Gay,^{7,19} who investigated 170 cases, gave the allergic classification a rating of 20 per cent, as compared with 30 per cent of cases attributable to foci of infection, 18 per cent to psychogenic factors, 5 per cent to endocrine dysfunctions, and 25 per cent to undetermined etiology. While Hopkins and

Kesten²⁷⁵¹ were, in general, unable to determine the causes of urticaria, they did find evidence of food allergy in about one fifth of 214 cases

We should like to emphasize meanwhile that every effort must be made—and the latest in vestigative methods employed—to determine the mechanism involved in order that a

TABLE 60—*Etiologic Factors in Urticaria*

Causation		Number of Cases			
		Male	Female	Both Sexes	Group Total
ALLERGIC BASIS					
Exogenous factors	foods	37	62	99	117
	drugs	4	7	11	
	injections serum	0	3	3	
	tuberculin	0	1	1	
	animal stings	0	3	3	
Endogenous factors	autosensitization	7	7	14	23
	menstruation pregnancy	0	9	9	
PATHERGIC BASIS					
Physical agents	cold	5	22	27	80
	heat	13	4	17	
	mechanical	1	13	30	
	exertion		4	4	
	light		2	2	
Infections	systemic	2	7	9	29
	focal	10	10	20	
Digestive disorders	acute gastro enteritis	18	26	44	169
	chronic gastro enteritis colitis	35	57	92	
	gastric anacid ty	2	9	11	
	gastric hyperacid ty	2	1	3	
	constipation	5	2	7	
	diseases of liver gallbladder	5	3	8	
	alcoholism	3	1	4	
Endocrine disorders	hyperthyroidism	0	6	6	7
	tetany	0	1	1	
Psychic factors		5	18	23	23
UNKNOWN BASIS					
Undetermined factors		25	27	52	52
Total		195	305	500	500

It is often very difficult, of course, to prove in a given case whether the urticaria is of allergic or pathergic causation. This question will be discussed in some detail below.

suitable therapeutic approach may be adopted. Moreover, it must always be borne in mind that, in both the allergic and the pathergic forms of urticaria, not only the allergen or pathergen but also the factors predisposing to allergy or to pathergy must be identified, if a lasting cure is to be achieved.

²⁷⁵ HOPKINS J. G. and KESTEN B. M. Arch. Dermat. & Syph. 29: 358, 1934.

a) ALLERGIC URTICARIA

Wolff-Eisner, in 1906, was the first to express the considered opinion that urticaria is to be regarded as an expression of an allergic state. Countless cases have since been reported in which the allergenic agent was identified beyond question, either by means of avoidance and exposure tests, or by the

treat gastro-intestinal disturbances and infections (Table 61). This approach of simultaneously attacking the allergy-predisposing and the allergy-precipitating factors is, as yet, insufficiently employed. Failure to give due consideration to the various predisposing factors (Fig. 346), is unquestionably one of the main reasons why treatment limited to ex-

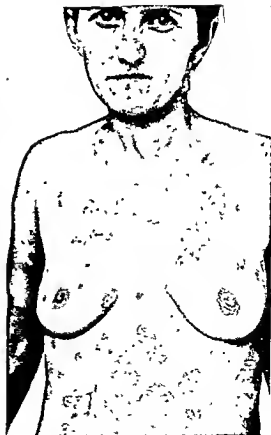
TABLE 61—*Eliciting and Predisposing Factors in Urticaria Due to Foods*

Eliciting Factors	Predisposing Factors	Number of Cases		
		Male	Female	Total
Proteins	not determined	29	43	72
	gastric anacidity	2	6	8
	gastric hyperacidity	2	0	2
	gastro-enteritis	4	9	13
	tonsillitis	0	2	2
Carbohydrates		0	2	2
Total		37	62	99

Prausnitz-Kuestner method. Since we could not possibly undertake to discuss all the possibilities, we shall present a summary according to the following outline. (1) exogenous allergens as a cause of urticaria, acting by (a) ingestion (foods, drugs), (b) injection or insect stings, (c) inhalation, (d) percutaneous contact, (2) endogenous allergens as a cause of urticaria, acting as (a) primary endogenous allergens, (b) secondary endogenous allergens.

(1) *Urticaria Due to Exogenous Allergens*

Ingestants.—An appreciable percentage but by no means the majority of all cases of allergic urticaria are attributable to hypersensitivity to food. In principle, any and every animal and vegetable protein, as well as carbohydrates, fats, salts, acids, and spices, can act as an urticariogenic agent. In 72 cases it was possible to demonstrate the presence of an uncomplicated proteinogenous hypersensitivity, either to animal or to vegetable protein. In other cases, however, the mere elimination of the guilty food from the diet or the administration of the indicated propeptan was not sufficient; it was also necessary to control the coexistent anacidity or hyperacidity with appropriate diets or drugs, and to

FIG. 346 CHRONIC URTICARIA DUE TO MILK
Appearing only during attacks of enteritis

clusion of the given nutritive allergen or to administration of propeptans is bound to fail.

Drugs taken by mouth can likewise—although far less commonly than foods—bring on urticarial manifestations. For details the reader is referred to the section on drugs (p 323).

Lastly, as shown by the ingenious experiments of Rappaport and Hoffman¹⁰⁴⁸ urticaria can also be caused by the nonproteinogenous components of foods such as the aliphatic nonconjugated aldehydes produced by the oxidation of fatty oils in the frying of foods and absorbed by the intestinal tract.

Injectants—That injection of foreign serum elicits urticarial manifestations in a large percentage of patients constitutes a well known phenomenon in serum sickness. The frequency with which penicillin causes urticaria has been mentioned elsewhere (p 335). More over many individuals react with local and sometimes even extensive wheal formation to insect stings and bites (bee wasp flea bed bug etc). According to Goldman²⁷⁵⁹ urticaria is occasionally observed in patients with scabies. Furthermore insulin and liver and other organ extracts not uncommonly evoke hives sometimes however the eruption is caused by the oily vehicles of various endocrine preparations. Moreover urticarial manifestations have been observed after subcutaneous and intramuscular injections of a great number of drugs.

Urticarial lesions appearing either during or immediately following blood transfusions may of course be due in some instances to passive transfer of the donor's antibodies. On the other hand the donor's blood may contain traces of food proteins to which the recipient is hypersensitive. Thus Stewart and Bates²⁷⁵³ reported a case in which the donor had eaten cockles the night before giving a transfusion to a patient who it developed was markedly hypersensitive to any type of shellfish. Even pooled human plasma may do the same as shown by Dickstein²⁷⁵² in the case of a patient sensitive to milk beef and lamb.

Inhalants—The significance of inhalant allergens in the production of hives has not as yet been fully appreciated. Outstanding

among these inhalants are feathers cotton kapok silk various kinds of dust flour animal danders pollen orris root the scents of flowers nasal sprays (including ephedrine) insecticides dyed materials and chemicals such as paraphenylenediamine. It appears likely that inhaled substances are absorbed through the respiratory tract and then distributed hematogenously to the skin. The senior author saw a case of extreme hypersensitivity to fish in which the mere smelling of the odor of fish was followed by the appearance of urticaria. Another patient was a middle aged woman whose hives occurred not only from eating buckwheat but also from touching or even inhaling it merely entering a room where someone was working with buckwheat was sufficient to produce urticaria. A case of chronic recurring urticaria of six years duration due to inhalation of perfume was reported by Zakon and Kahn.²⁸⁷ Derbes and Engelhardt²⁸⁸ described an instance attributed to ragweed pollen and therefore strictly seasonal and another due to the fumes of fresh paint and associated with asthma. A case reported by Rappaport and Hoffman¹⁰⁴⁶ is particularly interesting and enlightening urticarial manifestations occurred when glycenn treated cigarettes were smoked and the patient was found to be hypersensitive to acryl aldehyde formed as a by product during the burning of these cigarettes. Vaughan²¹ observed a woman who developed urticaria when smoking or even on entering a room where others were smoking.

Contactants—Although urticaria is fundamentally due to hypersensitiveness of the cutaneous blood vessels it is important to bear in mind that it may be elicited in rare cases by epidermal contact with certain agents. It may well be that substances so applied reach the cutaneous blood vessels by way of the cutaneous lymph channels. A few examples of contact urticaria will be cited.

Samson²⁷⁵¹ described a case due to hypersensitivity to cat hair. Lord¹⁴⁰ a case due to sheep's wool and Herrmann Sulzberger and Baer²⁷⁰⁶ instances due to silk and wool but not from all garments made from these fabrics and not on every exposure to the offending garments. Sulzberger also mentioned patients in

²⁷⁵⁹ GOLDMAN L. *War Med* 5: 794 1944

²⁷⁵² DICKSTEIN W. and BATES T. *Lancet* 1: 39 1938

²⁸⁷ ZAKON I. W. *Med. A. N.* 22: 1483 1926

whom the application of certain protein allergens by the usual scratch test technic elicited urticarial reactions, not only at and around the site of the scratch, but whenever and wherever the allergen-containing fluid touched the grossly unbroken skin surface as the droplet happened to run down the back or arm from the site of the test. Other cases of "contact urticaria" described by him include a barman with urticaria of the hands, within a few minutes after contact with orange and grapefruit, and of the perioral regions when orange juice was drunk; bakers with involvement of the hands on contact with wheat flour; patients reactive to contact with carrots, and a nurse with marked whealing of the skin after droplets of therapeutic solutions of arsphenamine or neocarsphenamine touched its surface. He states that in adults the eyelid areas, hands, feet, perioral, perianal, and genital areas seem to be particularly prone to contact-urticarial responses. Baagoe⁶⁹⁷ reported that an asthmatic patient who was hypersensitive to horse dander regularly developed urticaria on the inner aspects of the thighs after a horseback ride. Taub and White¹⁹⁷ investigated an instance of pollen urticaria without hay fever in a young woman who had positive scratch tests but negative mucous membrane tests; the condition failed to appear when the patient avoided golf courses and tennis courts. Shelnire⁷¹⁷ described urticaria due to contact with camomile (*Anthemis cotula*) and golden crownbeard (*Verbesina encelioides*). The senior writer has observed hives due to contact with lemon peel. Peshkin was able to ascertain that hives on the hands and forearms of a druggist were due to contact with emetine. The junior author has seen a woman with urticaria each time she applied ammoniated mercury ointment to her child's skin. Adelsberger found that an urticarial eruption was due to occupational contact with casein dye. Stokes⁷⁷⁰ mentioned the case of a man in whom urticarial wheals developed, two on each cheek, fifteen minutes after being kissed by his wife, who had just applied a new brand of lipstick. Sulzberger²¹⁵⁶ is of the opinion that dyes are not infrequently a cause of urticarial eruptions: 2 of his chronic patients were

relieved when exposure to a dye ceased. In addition, mouth washes, douches, and nasal sprays, as well as cosmetics, must always be kept in mind as possible urticariogenic contactants.

In all these cases, the restriction of the urticaria to sites of contact with the allergenic substances, as well as the positive patch tests, clearly indicate that the action took place by way of external contact and not by inhalation.

Contact with foods rather infrequently evokes urticaria. Joltrain, Brabant, and the senior writer have each observed 1 case of urticaria of the hands caused by contact with egg white while heating eggs. Vaughan²¹ saw a woman who had attacks of urticaria only at night, she proved to be allergic to corn, and the excitant was found to be the starch in her sheets.

It is well known that hives are quite commonly caused by contact with the setae or hairs of certain caterpillars, notably those of the *Bombyx* species, the procession caterpillars, the browntail moth, and others. On the other hand, it does not seem to be generally realized that urticaria can also be caused by the air-borne hairs of these caterpillars at the time of their transformation to the chrysalis stage (Merklen). D'Ingianni²⁷⁴⁶ found that lesions can be produced by the toxin glands as well as the caterpillar hair, while Steele and Sawyer²⁷⁵⁷ extracted an active principle from the browntail moth caterpillars, from the adult moth, and from the nests. Hyposensitization with this material was successful.

(2) Urticaria Due to Endogenous Allergens

The writers are convinced that endogenous allergens play a considerable part in the causation of urticaria. A distinction should be made between auto-endogenous and hetero-endogenous allergens. The former are understood to include blood or tissue protein that has been rendered foreign to the body and has thus become an endogenous allergen capable of eliciting an urticarial reaction; this heterogenization of the protein is usually a result of operation, scalding, traumatic san-

²⁷⁴⁶ D'INGIANNI, A. • New Orleans *MI & S J* 96 355, 1944

²⁷⁵⁷ STEELE, C. W., and SAWYER, W. H., JR. • Maine *MI A J* 35-137, 1944

⁷⁷⁰ STOKES, J. H. : discussion to Sulzberger et al.²⁰⁸

guneous extravasation or other physical injury. In view of the very great number of operations and accidents that take place and in view of the fact that urticarial cases of this kind are only rarely encountered it must be concluded that antibodies to autogenous protein are produced only under very special conditions. Particularly worthy of note in this connection is a case seen by us an urticaria that had stubbornly resisted all therapy disappeared on the very day on which a previously undiagnosed hydatidiform mole was found and removed. According to Joltrain⁵⁹ this category might also include cases due to as yet only vaguely defined products of fatigue formed in the tissues in the course of physical overexertion and reaching the circulation. Urticarial conditions sometimes arise in association with processes involving extensive cell disintegration such as gout or lymphogranulomatosis.

The group of allergies caused by primary or secondary endogenous agents likewise includes at least some of the cases of urticaria arising during the menstrual period during pregnancy or as a result of hyperthyroidism or tetany. It is as yet very difficult—not to say impossible—to determine in a given case whether the condition is due to allergy (antigen antibody reaction) or to nonallergic hypersensitiveness to a toxic substance (e.g. menstrual toxin). This problem is discussed in some detail in chapter XXXIII.

Intestinal worms (*ascari taenia oxyuris trichocephalus ancylostoma echinococcus*) may be regarded as hetero-endogenous allergens when their elimination is followed by immediate cessation of urticarial attacks (Fig. 347). We are inclined to attribute a similar role to bacteria in cases in which eradication of a focus of infection is promptly followed by disappearance of the hives. A few examples may illustrate this point. Rubritius reported on 5 cases of *Bacillus coli* infection of the urinary tract in which the urticaria ceased when the infection was overcome. Schur achieved immediate and lasting cessation of urticarial manifestations by cholecystectomy in 2 cases of biliary tract infection with recurring attacks of urticaria. Eagle⁷⁵³ stated that in the case of infected

cysts of the maxillary sinus which are sometimes the cause of urticaria puncture of the cyst with release of its contents will alleviate the symptoms temporarily but only complete surgical removal of the cyst will cure the cutaneous manifestations. In the same general category is an instance of urticaria that apparently represents a local response to bacteria (Fig. 348). The interesting feature is the annular configuration of the urticarial reaction surrounding each papulovesicular lesion. Urticaria due to fungous infection of



FIG. 347. URTICARIA CAUSED BY INTESTINAL PARASITES (ASCARIDES).

the feet was described by Wise and Sulzberger⁵⁹ and Waldbott and Ascher.^{2,60}

b) PATHERGIC URTICARIA

We shall here enumerate the pathologic conditions and abnormal metabolic processes often found in conjunction with urticaria. Appropriate studies are necessary in each case to determine whether they act by means of

⁵⁹ WISE F. and SULZBERGER M. B. J. A. M. A. 9: 1304 1940.
 WALDBOTT G. L. and ASCHER M. S. A. J. Dermat. & Syph. 36: 314 1933.

⁷⁵³ EAGLE W. W. South M. J. 3: 908 1934.

their toxic products, or by formation of endogenous allergens, or, as is very frequently the case, as predisposing factors.

Gastro-intestinal Diseases

Here we must distinguish between a number of different conditions. In occasional instances, hyperacidity is the only cause of an urticaria, as shown by the prompt disappearance of the cutaneous manifestations after appropriate dietary and therapeutic management, and by the reappearance of the urticaria



FIG 348 BACTERIAL ALLERGY

Spontaneous urticarial response surrounding each lesion in patient with recurrent papulovesicular eruption for eighteen months. Culture of lesions yielded *Staphylococcus aureus haemolyticus*. Focus of infection was probably chronic suppurative otitis media. Urticaria can be explained on basis of hetero-endogenous allergy to the bacteria.

when the acidity again rises. A far more common cause, however, is marked hypoacidity or anacidity. In such cases, not only the lack of hydrochloric acid itself but also the resulting changes in the chemistry and flora of the intestine are of importance.

In still other and by no means uncommon cases, abnormalities of the gastric acidity are the factors predisposing to food allergy. This should be borne in mind because adequate treatment requires not only management of the secretory disturbance or of the

nutritive allergy alone, but also measures designed to combat both factors.

The next and much larger group of conditions comprises gastritis and enteritis. Both the acute and the chronic forms are of great importance. Acute enteral processes, usually caused by food poisoning, and characterized by nausea, vomiting, generalized abdominal pain, diarrhea, and marked malaise, are often followed by urticaria. The latter may be induced by the toxins themselves, or by resorption of tissue protein altered as a result of the damage to the gastro-intestinal mucosa, or by absorption of undigested or partially digested food through the inflamed lining membranes. In this connection it should be mentioned that severe attacks of urticaria are frequently brought on by overindulgence in alcohol, causing gastritis and enteritis, and thus furthering resorption of insufficiently digested food proteins. An even larger number of cases are based on chronic irritation of the gastro-intestinal tract. The fact that chronic enteritis can be the underlying cause of hives has received scant attention and is indeed little known. This disease picture manifests itself by the presence of numerous fatty acid crystals and soapy globules in the stool, as well as by rapid elimination of the barium meal, which in these cases reaches the large intestine within about two hours. Good therapeutic results can be obtained by adherence to a bland diet consisting essentially of milk and free of all cellulose containing foods (FIG. 349).

Another condition to be included here is colitis, which may be a cause of intestinal putrefaction and fermentation. What has been said about the gastritides applies equally to the colitides: namely, in some instances the eradication of the intestinal disease may, in itself, serve to put an end to the urticarial condition (FIG. 350). In other cases, however, the mechanism is somewhat different. Incompletely digested food proteins may be resorbed through the inflamed colonic mucosa, thereby allergizing the organism; hence, when adherence to an appropriate colitis diet does not suffice to clear up the urticaria, it may be assumed that there is also a food allergy that may be controlled by specific propeptans or other appropriate therapy.

Finally, urticaria may involve the gastric

mucosa itself as reported by Chevalier²⁷⁶¹ Gastroscopy revealed changes varying from acute edema to local or generalized atrophic gastritis. In his opinion the cutaneous and the mucosal manifestations are frequently concomitant symptoms produced by a single agent.

Furthermore constipation is to be considered among the intestinal diseases and attempts should be made in every case to correct it by means of appropriate dietary regimens.

In occasional instances urticaria may be attributable to pancreatic insufficiency. Thus Markel⁶ reported a case in which treatment consisting only of oral administration of insulin free pancreatic extract brought relief from symptoms. For years the writers have been treating similar cases with large doses of hydrochloric acid plus pancreatin if the skin manifestations disappear the pancreatin is omitted in order to determine to what extent the pancreas is taking part.

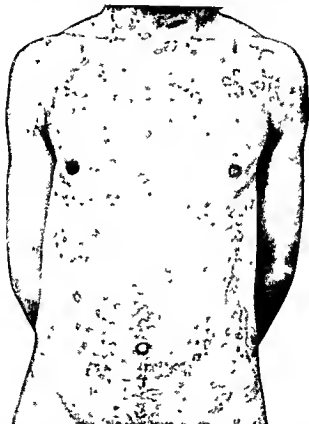


FIG. 349. URTICARIA ON BASIS OF INFLAMMATION OF SMALL INTESTINE

A quick decision as to whether or not constipation plays a role in a case of urticaria can be reached by observing the results of colonic irrigations. Sometimes, however the latter procedure may be followed by a rather violent although transitory outbreak of hives, presumably due to the increased absorption of the noxious agents by the mucous membranes.

Liver and Gallbladder Diseases

In a number of cases of refractory urticaria Shay,²¹⁸ Schur,²⁷⁶³ Daniel²⁷⁶⁴ Urbach²⁶⁵ and others found diseases of the liver and/or gall bladder appropriate treatment of which resulted in cure of the cutaneous condition. According to Shay, as well as Daniel decholin

²⁷⁶¹ MARCEL J. Arch. Dermat. & Syph. 39: 992, 1939.

²⁷⁶² SCHUR H. Wien. klin. Wochenschr. 40: 81, 1927.

²⁷⁶³ DANIEL J. A. ch. d. mal. de l'app. digestif 22: 30, 1932.

²⁷⁶⁴ URBACH E. A. ch. f. Dermat. u. Syph. 175: 767, 1937.

²⁷⁶⁵ CHEVALLIER P. and MOUTON F. Ann. de dermat. et syph. 7: 337, 1936.

is especially useful. We must not fail to mention, however, that in our experience some cases of liver and gallbladder disease (manifested on the one hand by icterus, on the other by biliary colic) are not the underlying causes of the urticaria, but rather another clinical expression of the same mechanism. An instance of urticaria and severe gallbladder crises, which could be simultaneously evoked by ingestion of lobster with mayonnaise, is fully described, with cholecystograms, on page 686. In another patient, jaundice became

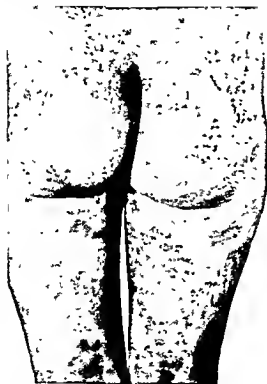


FIG 350 URTICARIA THAT DISAPPEARED AFTER CURE OF COLITIS

manifest eight days after the urticaria first appeared.

Diseases of the Urinary Tract

Conditions of the urinary apparatus, particularly of the kidney and renal pelvis, as well as of the bladder, may be causes of urticaria, either in themselves or as a result of secondary infection.

Metabolic Disorders

Of all the metabolic diseases, diabetes especially turns out to be the overlooked cause of

occasional cases of chronic recurrent urticaria, such an oversight is especially likely when the urine is negative for sugar and the fasting blood sugar level is normal. Whenever the etiology of urticaria is obscure, a glucose tolerance test should be performed. However, there are a few cases in which the tissue carbohydrate tolerance, as demonstrated by an increased skin sugar content, is impaired despite normal blood sugar curves on testing (Urbach⁷⁷⁴). Since the determination of cutaneous glucose requires a biopsy of the skin, to which some patients will not submit, a simple clinical test may be substituted. This consists of a brief adherence to a strict diabetic diet (three to four days), combined with administration of small doses of insulin (5 units subcutaneously, three times daily). If the urticaria disappears after this procedure, "skin diabetes" may be assumed. It is interesting to note that this condition is chiefly found in persons over 45 years of age, characterized by a peculiar purplish color of the cheeks and by obesity, and likely to be of the Jewish race. Proceeding in this way, the writers succeeded in curing a number of previously refractory cases of chronic urticaria.

Occasional cases of urticaria have been found to be due to gout. In one instance, the senior author—by means of chemical determinations of uric acid in the blood and skin—succeeded in bringing definite proof to this effect.

A number of authors, headed by Schreus,⁷⁷⁶ hold that an appreciable percentage of all cases of urticaria are due to disturbances of the acid-base equilibrium, particularly acidosis. Without wishing to enter into a discussion here as to whether these metabolic disturbances are primary or coordinate, we can state that in our own experience, as well as in the previously expressed opinions of Solomon and von Noorden, of Dinken, and of McCaskey,⁷⁷⁷ alkaline therapy is frequently very useful and sometimes even effects a permanent cure. This classification also embraces the so-called sweat urticaria of Marchionini and Ottenstein.⁷⁷⁸ In this condition hives are evoked

⁷⁷⁴ URBACH, H. T. *Muenchen med. Wchnschr.* 75, 340, 1928.

⁷⁷⁵ MCCASKEY, G. W. *J. Lab. & Clin. Med.* 7: 334, 1922.

⁷⁷⁶ MARCHIONINI, A., and OTTENSTEIN, B. *Klin. Wchnschr.* 10: 969, 1931.

by profuse sweating, and an attack can also be elicited by an injection of pilocarpine. Alkaline diets are likewise beneficial here.

Endocrine Gland Disturbances

These play an important rôle in urticaria, particularly in women. The possible influence of the menopause, as well as of menstrual disturbances (amenorrhea, dysmenorrhea), must be considered, and the indicated substitutional therapy should be instituted to combat it. (For a more detailed discussion of menstrual allergy, the reader is referred to the relevant section, p. 855.) Furthermore, tests of thyroid function must be performed on patients of both sexes, since hyperfunction of the thyroid gland is not rarely a factor, at least in promoting allergy. The writers have repeatedly observed that hyperthyroid patients tend to suffer severe attacks of hives, and that often these urticarial attacks do not cease until the thyroid disease is cured. It is interesting to note that in 2 of our cases, the first urticarial manifestations made their appearance after roentgen irradiation of the thyroid gland; this is probably to be interpreted as an expression of allergization brought on by altered thyroid proteins acting as endogenous allergens. Loew,²⁷⁶⁹ on the other hand, reported the appearance of urticaria and an angioneurotic edema following thyroidectomy, with a postoperative basal metabolic rate of -12; the cutaneous manifestations responded favorably to the administration of 1 mg of thyroxin, and reappeared when this medication was interrupted. Epstein²⁷⁷⁰ believes that urticaria and angioneurotic edema are more commonly associated with hypothyroidism than with hyperfunction. We observed a case in which a severe attack of urticaria followed the inadvertent removal of a parathyroid gland during thyroidectomy; the urticarial condition failed to manifest itself as long as parathormone was administered.

One thing is certain: the development of urticaria is dependent upon a certain degree of lability of the neurohormonal regulatory mechanisms, although the manner in which imbalances of this system occur may vary of course from case to case. This explains the

far higher incidence of urticaria among adults than among children, its relatively greater frequency among women than among men, the commonly observed association of urticaria with angioneurotic edema and migraine, especially in women, and the well-known dependence of urticaria—of whatever origin—on menstruation, emotional upsets, and similar factors.

Bacterial Infections

Another group of conditions of etiologic importance in the production of urticaria are the infections; these should be divided into general and local types. The general infections, such as grippe and rheumatism, are to be regarded as paving the way for rather than actually causing urticaria. The question as to whether the urticariogenic influence of the infections is based on toxicity or allergy has not as yet been answered; the situation is all the more obscured by the fact that, especially in acute infections, the results of skin tests with bacterial substances are very frequently negative. Parenthetically, it should be pointed out that when urticaria appears in conjunction with infectious diseases, the possibility of its being due to antibiotic or chemotherapeutic agents, or other medication should be carefully evaluated.

On the other hand, focal infections, particularly in the tonsils, sinuses, and teeth, as well as in the appendix, gallbladder, bladder, and elsewhere, frequently constitute the only etiologic factor, and the removal of such foci effects a rapid and lasting cure of the urticaria (Fig. 351). Numerous examples of this sort have been observed, of which we will cite here only Lenche's²⁷⁷⁰ report of 2 cases of urticaria due to meat in which removal of inflamed appendices eradicated the hypersensitiveness. In cases of uncertain etiology, the possibility of a hypersensitiveness to pathologic intestinal flora must be considered, and appropriate investigative measures, sometimes including tests with autogenous stool vaccines, must be undertaken. In short, every case of chronic urticaria should be carefully investigated—by specialists whenever necessary—for any possible focal infection.

²⁷⁶⁹ LOEW, H. and KRAEMER, H. *Med. Klin.* 30: 1494, 1934.

²⁷⁷⁰ LENCHE, R. *Presse med.* 44: 916, 1936.

To minimize the possibility of overlooking any such focus, we employ a special table listing the investigations to be undertaken (Appendix).

Needless to say, it does not necessarily follow that every infected tooth or tonsil is etiologically associated with an existing urticaria; nevertheless it is always advisable, when conservative measures prove inadequate and when surgical intervention is not contraindicated, to eliminate the focus by means of

organ; this attack, however, is sometimes the last one.

In cases in which infection of the intestinal tract can be bacteriologically proved, it is advisable to administer an autogenous stool vaccine. Good results with this method have been reported by Emmet and Logan,²⁷¹ Hopkins,²⁷² and Traut.²⁷³ Cultures from duodenal drainage are occasionally useful (Hansen Pruess²⁷⁴). In a few cases in which intestinal infection was thought to be the



FIG. 351 URTICARIA DUE TO DENTAL FOCAL INFECTION

operation. One must not expect, however, that eradication of the infection, even when it is the cause of the urticaria, will bring immediate results, especially in cases in which it is the allergy-predisposing and not the allergy-precipitating factor. It is advisable in every case to prepare an autogenous vaccine from the focus and to inject this vaccine at intervals of from three to five days. A renewed and severe attack of urticaria is not infrequently observed after surgical intervention in a suppurative focus or operation on an infected

dominating cause, Rockwell had appreciable success with succinylsulfathiazole (0.033 Gm. per pound of body weight every four hours for two to seven days).

Systemic Diseases

In some cases it is impossible, despite the most painstaking investigation, to determine

²⁷¹ EMMETT J. L. and LOGAN, A. H. J. A. M. A. 101, 1966, 1933.

²⁷² HOPKINS J. G. New York State J. Med. 38, 23, 1938.

²⁷³ TRAUT, E. F. Arch. Dermat. & Syph. 40, 368, 1939.

²⁷⁴ HANSEN PRUESS, O. C. J. Allergy 9, 377, 1938.

the cause of an urticaria. Sometimes especially when the patient steadily loses weight the possibility of cancer must be borne in mind. In other instances urticaria is a premonitory symptom of pernicious anemia or of an affection of the hematopoietic system (leucemia lymphogranulomatosis).

Psychic Factors

Psychosomatic influences are not uncommonly the underlying cause of urticaria. Stokes, Kulchar and Pillsbury,⁹ who in

A distinction must be made between various types of psychogenic mechanisms. There is not the slightest doubt in the mind of any clinician that hives are influenced by worry, excitement and other emotional upsets. However this sort of emotional background is not under consideration here. We are referring to those cases in which to all appearances the psychic trauma constitutes the only etiologic agent. It is to be noted in this connection that the psychosomatic element is more important in women than in men. Obviously

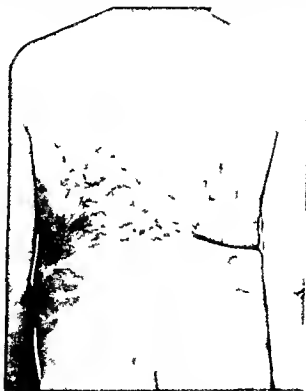


FIG. 352. URICARIA ON PSYCHIC BASIS

investigated the pathomechanism of urticaria in a large number of cases by means of the most modern methods found that in 12 per cent psychoneurogenous disturbances were the only responsible factor while playing at least a contributory role in no less than 83 per cent. Similarly in a series of 25 cases of chronic urticaria Wright⁵ found that in 70 per cent some definite shock, worry or nervous exhaustion preceded or accompanied the onset of the illness.

It is not easy to find definite proof of the fact that a case of urticaria is due solely to some inner conflict. In some instances of heat urticaria any emotion may bring on renewed attacks of hives; under such circumstances the psychic element cannot be considered as the primary cause of the urticaria since it operates by way of its effect on the heat regulating mechanism. Moreover there are some cases—not a rarity by any means—in which as a result of psychologic conditioning the primarily allergic urticaria persists long after exposure to the excitant has ceased.

But even when consideration is given to all these possibilities, there remain some cases that may be regarded as psychogenic in origin. The writers have had occasion to observe a number in which a previously refractory urticaria disappeared after the settlement of a grievance, or after changes in certain psychic conditions. It is noteworthy that these patients in particular attempt to dissemble and to deny the existence of a psychic factor. Thus, the writers observed the case of a highly intelligent but distinctly masculine woman whose chronic urticaria persisted stubbornly until she finally made up her mind to break her engagement (FIG. 352). Another pertinent example was that of an elderly man who had hives as the result of grief over the way his sons were neglecting him; many weeks of intensive treatment were of no avail. Finally, after a frank discussion of the situation, followed by a change in attitude on the part of the sons, the old man's condition rapidly improved and was soon cured. Careful investigation to determine the nature of the psychic background, and an explanation to the patient of the relationship between emotional disturbances and urticaria, are more likely to bring relief than is a purely allergic approach followed by treatment along the usual lines, according to Farquharson.^{277a}

Physical Factors

In our material, a strikingly high percentage of cases fell under the classification of urticaria due to hypersensitivity to physical agents (80 of 500 patients). These somewhat surprising figures may be explained by the fact that in every one of these cases—regardless of whether or not the history seemed to call for them—systematic tests were performed for hypersensitivity to cold, heat, sweat, pressure, exertion, and light. While these tests are simple in themselves, there are some pitfalls that must be avoided. Thus, the mere performance of the cold water test does not by any means conclude the investigation concerning the possibility of cold urticaria. For it must be noted that some patients are hypersensitive not to cold water but to cold air, or vice versa, while still another group manifests

cold hypersensitivity only of certain parts or areas of the body. Rajka actually observed a case of fixed type (i.e., hypersensitivity confined to a definite site). Similar observations have been made in relation to heat urticaria. For example, a negative response to contact with a test tube filled with hot water, and a manifest reaction to exposure to heat (e.g., sitting near a hot stove), and vice versa.



FIG. 353 EFFORT URTICARIA EXPERIMENTALLY EVOKED BY STRENGTH'S PHYSICAL EXERTION

Furthermore, cases have been described in which whealing is not elicited by application of heat or radiant heat (e.g., proximity to a hot stove), while urticarial manifestations are evoked by exertion (e.g., ascending stairs, mountain climbing): the latter condition is known as effort urticaria (FIG. 353). Another special clinical type is sweat urticaria. The diagnosis can be made on the basis of the patient's history that hives appear only after perspiration. Clinically it is characterized by small individual lesions of follicular distribution (FIG. 354). For test purposes, perspira-

^{277a} FARQUHARSON, R. F.: *Illnesses M. J.* 80: 454, 1941.

tion may be induced by vigorous exercise or an injection of pilocarpine. That type in which symptoms follow exercise, emotional stress or exposure to heat and in which injections of acetylcholine (methyl chloride) or pilocarpine induce attacks identical with the spontaneous ones has been called cholinergic urticaria by Hopkins et al.⁵⁷⁷ It is possible that these drugs act through the parasympathetic nervous system to release H substance.

The test for light urticaria is made by exposing the patient to natural sunlight. These cases are often less sensitive than normal individuals to the artificial ultraviolet rays of quartz lamps.

tion of firm pressure by means either of a heavy weight or of vigorously pinching the skin. Cases of true pressure urticaria not infrequently fail to manifest the slightest reaction to mere rubbing.

Lastly, all possible combinations have been encountered. Both cold and heat have been observed to evoke reactions in the same individual. In others urticaria was elicited by cold pressure rubbing but not by heat, and so on. Cases of the latter kind, which are by no means rare, tend particularly to arouse doubt as to the specific allergic character of urticaria due to physical stimuli; we⁵⁸⁸ are inclined therefore to include most of them among the



FIG 334 SWEAT URTICARIA

While urticaria recurring only in warm weather suggests sensitivity to heat or sunlight, the following differential possibilities should be borne in mind: allergy to pollen, fungi, insect bites, foods ingested only in the summer, and drugs used primarily in the summer, either internally or externally, and rarely an urticarial id reaction in dermatophytosis. A careful history, tests with physical agents, and appropriate investigative procedures should clarify the diagnosis.

In pressure urticaria, one must be on the lookout for a delayed reaction that occasionally appears hours—even as much as twenty-four hours—after the test (Urbach and Fasal⁷²⁵). Moreover, differentiation must be made between urticaria factitia and pressure urticaria; the former can be evoked by gentle rubbing or stroking of the skin, while the latter makes its appearance only on applica-

vasoneuropathies. On the other hand, there have been a few carefully observed instances in which the hypersensitiveness to cold, heat, or other physical agents could be passively transferred to normal recipients. While only a few such reports are on record, their infrequency is probably due to the fact that the antigens involved are most likely endogenous allergens—that is to say, substances released from the skin tissues by the physical influence (cold, heat, or pressure) and acting as antigens. This assumption seems to be proved by the fact that by means of the reverse Urbach-Koenigstein technic, Melczer and Wlassics⁶⁶ succeeded in transferring heat hypersensitiveness passively. The procedure in practice is as follows: a skin area of the recipient is exposed to fairly intense heat for example, and the content of a blister raised on the skin of the specifically allergic patient is

then injected into this site; a positive reaction takes the form of marked wheal formation.

However, although urticaria due to physical stimuli is sometimes of allergic origin, there are many instances in which allergy seems to play no part whatever. These are the cases in which the cure of a stomach disease or of an enteritis, the elimination of a focal infection (such as a granuloma of a tooth, tonsillitis, or appendicitis), of a worm infestation, or of an endocrine disturbance, is promptly followed by cessation of the urticaria due to cold, pressure, or other agency. Cases of this kind, as well as those in which there is no specific reaction to one physical agent, although the patient reacts with wheal formation to any number of different physical stimuli, should in our opinion be considered as vasoneuropathes—i.e., as nonspecific vascular responses. Needless to say, the differentiation between allergic and non-allergic causation in a given case of urticaria due to physical stimuli is of decisive importance for the therapeutic approach. It should be noted, however, that even in proved allergic cases of physical urticaria, the therapy must include, in addition to specific anti-allergic measures, the elimination of the factors predisposing to allergy (infections, toxic states, gastro-intestinal disturbances, liver damage, functional imbalance of the endocrine glands, psychosomatic influences).

In conclusion, brief mention must be made of urticaria factitia or *dermographism*, which not infrequently appears on the skin and very rarely on the mucosa (e.g., of the mouth, as reported by Vallery-Radot²⁷⁷) on gentle stroking with a blunt object. Here, too, opinions are sharply divided as to whether the manifestations are to be regarded as the expression of a pathergic or of an allergic reaction. Ebbecke, Goldscheider, and other authorities hold that wheal formation in response to mechanical irritation is nothing more than a pathologic exaggeration of the normal reaction, and can therefore not be regarded as allergic. Lewis and Grant assume that the condition is due to a histamine-like substance released from the tissue cells as a result of the mechanical

influences. Walzer,¹⁸⁶⁴ on the other hand, and Lehner and Rajka, champion the theory of the allergic character of this phenomenon, in view of their success in passively transferring the hypersensitiveness by means of the Prausnitz-Kuestner method. Since urticaria factitia is a rather common condition, we are of the opinion that an underlying specific-allergic mechanism is probable only in the most pronounced forms. The senior author for his own part, adhering strictly to the criteria mentioned on page 7, never succeeded in passively transferring this presumed hypersensitiveness, and is therefore of the opinion that urticaria factitia should be regarded as a pathergic reaction.

True dermographism should not be confused with "black dermographism," a purely physical phenomenon produced by stroking various metals on skin which has been in contact with powders, dusts, ointments, or pastes (Urbach and Pillsbury²⁷⁷¹).

3 ETIOLOGIC DIAGNOSIS

It is apparent from the diversified pathogenesis of urticaria that there can be no one method of determining the cause in any given case. One is therefore confronted first of all with the problem of ascertaining whether a case is due to an underlying allergy or pathergy. It is often very difficult to answer this question; yet every effort must be made to do so, since the therapeutic approach will depend upon the recognition of the true nature of the pathogenesis.

As for every allergic condition, a minutely detailed history must be taken, this frequently leads the physician onto the right track, or at least gives him some point of departure for further investigation. However, when no enlightening information is forthcoming, the physician must systematically, point by point, look for any and all possible causes, in the manner described in detail in the preceding section. When necessary, all the resources of modern internal, allergic, and chemical investigative methods should be employed; when no clues are available, one must attempt to arrive at a diagnosis *ex purantibus* by surgical removal of any suspicious focus.

²⁷⁷ VALLERY RADOT, P., KRIEY, J., and JACQUEMAIRE, R. *Presse méd* 32 517, 1924

²⁷⁷¹ URBACH, E., and PILLSBURY, D. M. *J. A. M. A.* 121: 485, 1943.

When underlying allergy is suspected one must avoid putting too much faith in the results of skin tests. The writers emphatically agree with Sulzberger and Rostenberg⁷⁷⁹ in rating all forms of skin tests as of very little value. Stokes and his associates⁷⁸⁰ found the scratch test to be unreliable in 50 per cent of their cases. Hopkins and Kesten⁵³⁴ arrived at a similar conclusion; they even found that in one large group consisting exclusively of patients hypersensitive to foods the ratio of dependable results was no greater than 10 per cent or at the most 20 per cent. Waldbott and Ascher⁷⁸¹ reported reactions in only 27 per cent of their cases. This may perhaps be explained by the fact that the urticaria is often evoked not by the suspected substance itself but by one of its metabolic products or derivatives or in other instances by the fact that the primary shock organ is not the skin but the mucous membrane for example that of the gastrointestinal tract (see p. 39). This is why the elimination diet or the propeptan diet (see p. 190) is far more successful than skin tests in food allergies.

On the other hand in cases of contact urticaria epidermal tests are recommended. In exceptional instances the urticaria is elicited by way of the nasal mucosa (primrose odor—von Hoesslin⁷⁸²) or by way of the conjunctiva (cat hair—Hopkins and Kesten⁵³⁴). In such cases mucous membrane tests are indicated.

It should be noted that the literature contains reports on specific and occasionally exceptionally strong reactions to intracutaneous tests. Thus Lehner and Rajka¹⁷⁷ described a case of urticaria due to acetylsalicylic acid in which an intracutaneous injection of this drug evoked not only a strong local reaction but also definite focal and general manifestations. These authors also observed a patient with urticaria who was hypersensitive to milk; on intracutaneous injection of 0.05 cc of aolan the patient responded not only with a local and focal reaction but also with a severe anaphylactic shock.

4 THERAPY

In view of the diversity of the etiologic factors there can obviously be no one standard

therapeutic approach to urticaria. It is equally apparent that the therapy must be individualized according to the indications after painstaking investigation of a case.

a) SPECIFIC THERAPY

When there is a known allergenic agent every effort should be made either to eliminate exposure to it or preferably to deallergize or hyposensitize the patient by means of the procedures discussed in chapter XII. Furthermore regardless of whether or not the allergen has been identified every case should be carefully studied for the possible presence of allergy predisposing conditions if such factors are found they should of course be appropriately managed by either medical or surgical measures. Stokes⁷⁸³ pointed out that attention to several factors in a case rather than to one alone increases the proportion of good results.

b) NONSPECIFIC THERAPY

Nonspecific therapy is to be undertaken only after the search for an allergic excitant as well as for predisposing and contributory causes has been thoroughly carried out and finally abandoned as fruitless. Nonspecific therapy embraces a great variety of approaches and methods and the procedures of choice among them depends in turn on certain features of the given case—including whether it is acute or chronic.

(1) Acute Cases

An attempt should always be made to empty the entire intestinal tract by means of castor oil and either a high enema or preferably a high colonic irrigation. Furthermore if an infectious intestinal element is suspected the patient should take creosote carbonate (20 drops) together with activated charcoal (1 to 2 Gm. or 15 to 30 grains) three times daily over a period of several days. The diet should be bland; coffee, tea and alcohol are to be avoided. To control intense pruritus or severe attacks of urticaria it is advisable to administer 0.25 to 0.50 cc. (4 to 8 minims) of 1:1000 epinephrine subcutaneously or if the relief is too evanescent 1.0 cc. of 1:500 epinephrine in oil intramuscularly. Repeated doses of ephedrine by mouth are also often effective. Frequently the symptoms can be

⁷⁷⁹ SULZBERGER, M. B. and ROSTENBERG, A. *J. Allergy* 6: 448, 1935.

⁷⁸⁰ WALDBOTT, G. L. and ASCHER, M. S. *ibid.* 9: 584, 1938.

⁷⁸¹ HOESSLIN, H. *On Nahrungsmittel-Webesch.* 81: 1799, 1934.

controlled by a series of intravenous injections of 10 per cent calcium gluconate, or preferably of the calcium bromide-thiosulfate solution mentioned on page 227. Pituitrin by injection sometimes gives amazingly good results, usually, however, only temporary. Atropine sulfate (0.25 mg., or 1/240 grain) injected subcutaneously, may well be tried. Venesection of 300 to 500 cc. is indicated if there are unbearable itching and severe headaches. Local treatment consists in the application of shaking lotions containing anesthesin (approximately 2 to 3 per cent) or 5 per cent of calmitol liquid:

R	Anesthesin	Gm or Cc	
	Zinc oxide	3 6	3i
	Talcum	aa 24 0	aa 5iv
	Glycerin		
	Alcohol, 70 per cent		
	aa q s ad	120 0	aa q s ad f3iv

Protracted lukewarm baths containing bran, starch, or oatmeal often give temporary relief. The addition of 5.0 cc. (1 dram) of a 25 per cent solution of menthol in alcohol to the tub of water often greatly increases the anti-pruritic effect; it causes a sensation of coldness of the skin, and patients should be advised to dry themselves immediately and go to bed for a short time.

(2) Subchronic and Chronic Cases

In addition to those just mentioned, the following measures may be useful here.

Even when a nutritive factor cannot be demonstrated, various diets are well worth trying in succession, devoting one week to each: in the first week, a diet completely free of animal protein; second week, a completely salt-free diet; third week, a definitely alkali-producing regimen (milk, cheese, potatoes, white bread, spaghetti, noodles, carrots, beans, peas, asparagus, bananas), supplemented by daily intravenous injections of 20 cc. of a 4 per cent sterile solution of sodium bicarbonate,* or large doses of alkalis by mouth. During the fourth week, an acid-ash diet may be tried (high protein content, no fat, no sodium chloride), together with 1 Gm. (15

grains) of ammonium chloride five times a day, or 0.33 Gm. (5 grains) of potassium chloride in 8 ounces of water three times a day (Rusk and Kenamore⁸⁷³).

Occasionally, good results are obtained by changing the intestinal flora by means of *Bacillus acidophilus* milk or a series of colonic irrigations containing activated charcoal. In cases in which the reaction of the stool was alkaline, Aitken²⁷⁸² gave copious amounts of buttermilk and lactic oats with good results.

Bray⁸⁸⁰ recommended histamine treatment, preferably by iontophoresis. Hajós gave 0.001 mg. of histamine subcutaneously, gradually increasing the dose to 0.1 mg. Alexander²⁷⁸³ employed the following schedule of dosage in chronic urticaria:

TECHNIC For the first two days 0.05 cc. of a dilution of histamine phosphate equivalent to 1/10,000 histamine base is given subcutaneously twice daily. For the next two days 0.1 cc. is injected, followed by 10 daily injections beginning with 0.15 cc. and increasing by 0.05 cc. each day. When a 1/1,000 dilution is used, injections are given every second day, commencing with 0.15 cc. and increasing by 0.05 cc. for each succeeding dose for 5 injections. Thereafter, a maintenance dose of 0.35 cc. is given every third day.

Alexander and Elliott³⁴⁸ also administered histamine intravenously with satisfactory results (for technic, see under Ménière's disease). While several authors reported favorable results with histaminase (torantil), their observations have not been confirmed.

Beneficial effects from a course of injections of histamine-azoprotein complex (bapamine) have been described by Cohen,⁸⁸² Saletta,²⁷⁸⁴ and Edrington.²⁷⁸⁵ As noted elsewhere, this substance should only be used with great caution.

The new synthetic antihistamine preparation benadryl (β -dimethylaminoethyl benzhydryl ether hydrochloride) is stated to be highly effective in doses of 50 to 100 mg. two to five times daily, by Feinberg and Friedlaender,⁶⁵² O'Leary and Farber,²⁷⁸⁶ and Pillsbury.²⁷⁸⁷ However, in the majority of cases

²⁷⁸² AITKEN, R. *Brit J Dermat* 51, 13, 1939.

²⁷⁸³ ALEXANDER, H. L. *Synopsis of Allergy*. St. Louis: Mosby, 1911.

²⁷⁸⁴ SALETTA, S. N. *Letters, Internat. Corr. Club of Allergy*, Series 7, 50, 1943.

²⁷⁸⁵ EDRINGTON, N. A. *ibid.*, Series 8, 3, 1944.

²⁷⁸⁶ O'LEARY, F. A., and FARBER, E. M. *Proc. Staff Meet.*, Mayo Clin. 20, 479, 1935.

²⁷⁸⁷ PILLSBURY, D. M. personal communication.

* Sterile, chemically pure sodium bicarbonate should be employed, dissolved in sterile water. The solution must not be boiled, but may be heated to a temperature of 63°C. Only a freshly prepared solution should be used.

relief is obtained only while the drug is being used. Larger doses rather often produce intolerance in the form of drowsiness, dizziness, weakness, dilatation of the pupils, and dryness of the mouth.

Autohemotherapy, 10 cc given intramuscularly twice weekly, or autoserotherapy, 0.2 cc injected intracutaneously on alternate days, should be tried in all refractory cases, particularly when there is reason to suspect the presence of endogenous allergy. Similarly, autogenous urine and the urinary proteoses (p. 123) have occasionally been found to be effective.

Cherfils²⁷⁸⁸ recommended roentgen irradiation of the spleen in a series of three to five treatments, to be repeated at increasing intervals (single dose 250 r with filter of 0.5 copper plus 1 aluminum). Strangely, the coagulability of the blood is increased under the influence of irradiation; moreover, Cherfils claims that the treatment has no therapeutic value unless this change appears.

Vegetative insulin shock was advocated by Bartelheimer.⁸³⁰ A subcutaneous injection of 30 to 40 units of insulin is administered; the urticaria subsides promptly with the outbreak of sweat and the occurrence of tremor, fatigue, and palpitation. The more pronounced the vegetative symptoms resulting from the hypoglycemia, the better the effect. Intravenous injections of 10 to 16 units of insulin may also be used, but should be avoided in hypotension and in cases in which the possibility of circulatory failure exists. Repeated administration of small doses of insulin once or twice a day is likewise effective in chronic urticaria.

The combination of nicotinic acid (20 mg twice daily with meals) and calcium lactate (0.3 Gm. or 5 grains three times daily with meals) was reported by Chambers and Benton²⁷⁸⁹ to produce marked improvement in a series of cases with giant urticaria within one to two days and complete clearing in three to four days. Thereafter, the dose of nicotinic acid was reduced to 20 mg daily for about ten days, then every second day for one month. Recurrences could be controlled by a repetition of the course. The present writers have

found this treatment of value, but not as beneficial as the above would suggest.

Menadione (synthetic vitamin K) in doses of 2 mg three times daily for from one to four weeks was found by Black²⁷⁹⁰ to relieve 62 per cent of a large series of cases of urticaria and angioneurotic edema which had failed to respond to the usual forms of treatment. Many were helped within two days of treatment and most within one week, although others required longer. The proportion of cures was far greater in patients whose prothrombin time was prolonged as compared with those with normal values. Readministration of vitamin K terminated all relapses.

In all cases of urticaria in which the patient's sleep is disturbed, effective soporifics may be given—provided, of course, that hypnotics do not appear to be contra-indicated by the history—as well as sedatives to be taken during the day, such as Bellergal (1 tablet) or phenobarbital (0.015 to 0.030 Gm. or $\frac{1}{4}$ to $\frac{1}{2}$ grain) three times a day. In refractory cases, small doses of ephedrine (0.025 Gm. or $\frac{3}{8}$ grain) along with phenobarbital (0.008 Gm. or $\frac{1}{8}$ grain) given three times a day over a period of weeks may bring lasting relief, and excellent results have occasionally been obtained with gynergen (1 tablet of 1 mg. two or three times a day).

That the psyche of the patient merits special consideration in urticaria has already been mentioned; a change in environment, especially a vacation in the mountains, is often beneficial.

c) TREATMENT OF URTICARIA DUE TO PHYSICAL STIMULI

It is imperative, above all, to recognize—and then to eliminate—the processes contributing to pathergization or, in other words, the factors predisposing or conditioning the individual to pathologic vascular reactions, for as shown on page 410, many permanent cures of physical urticaria have been achieved by elimination of an intoxication, eradication of an infection, correction of an endocrine dysfunction, and similar indirect therapy.

Lehner and Rajka recommend that specific desensitization be attempted in every case. This procedure, in cases of cold urticaria, for

²⁷⁸⁸ CHERFILS, J. *Tr. Fou. h. l. n. e. nat. Rad. et. Cong.* 2: 330, 1934.

²⁷⁸⁹ CHAMBERS, D. C. and BENTON, H. S. *J. Allergy* 15: 141, 1944.

²⁷⁹⁰ BLACK, J. H. *ibid.* 16: 83, 1941.

example, consists in exposing a fairly large skin site to the effects of cold once or twice daily; then, as the skin evidences reduced sensitivity to cold, increasingly large areas are exposed and possibly the duration of the exposure also is lengthened. The writers would like to add, however, that by no means all of the results achieved in this manner constitute permanent cures, and that a number of authors, especially Alexander,²⁷³¹ do not regard the decreased reactivity as a true deallergization or desensitization, but rather as an example of Ebbecke's exhaustion therapy.

In a case of hypersensitiveness to ultraviolet rays, W. Frei achieved a marked degree of insensitiveness by means of repeated brief irradiations with a quartz lamp.

In treating the contact type* of physical urticaria, Duke⁵⁶⁷ similarly attempted to produce at least a certain amount of tolerance by means of the systematic application of cold water in cold urticaria, by irradiation with the rays found to be injurious to the light urticaria patient, by exposure to the heat of a 1,500-watt nitrogen lamp in cases of heat urticaria, and in treating so-called mechanical urticaria by frequently brushing the skin with a stiff brush. Duke added, however, that these methods frequently prove disappointing, especially in cases of light, heat, and cold urticaria, and that it is then necessary for the patient to change his daily habits, his occupation, his manner of dressing, and sometimes even his habitat (especially as regards climate) in such a way as to find conditions of light, heat, or cold that he can tolerate.

In the reflex-like type,† in which the skin manifestations are generally accompanied by various systemic symptoms, a thorough study must first be carried out in order to determine whether or not any internal disease is responsible for the general symptoms. To raise the often incredibly low threshold of tolerance, Duke proceeded in the following manner. A reaction following brief application of heat is counteracted by immediate application of cold. Contrariwise, in cold urticaria, ice is applied

until the general manifestations begin to appear, at which point heat is immediately applied. These measures are repeated daily for a long period of time.

A number of patients have been observed to react strongly to heat and exertion when their body temperature is especially low. Duke⁵⁶⁷ reported that fever therapy is sometimes beneficial in cases of this kind, and that not only temporary relief but sometimes even permanent cures have been achieved in this manner. The fever is induced by subcutaneous or intravenous injections of *Bacillus coli*. Needless to say, this therapy must be administered most cautiously. Duke began treatment with 10,000 organisms, injected subcutaneously.

In cases not responding to other therapy, a course of histamine injections or of histamine-azoprotein (hapamune) injections (see above) may be tried cautiously. Preliminary observations by Feinberg and Friedlaender⁵⁵² indicated that benadryl is particularly effective in cold urticaria.

5. URTICARIA IN ANIMALS

As a supplement to the discussion above, brief consideration must be given to urticaria in animals, which occurs not altogether infrequently. According to Heller,⁷⁷² cattle, horses, and dogs develop hives owing to absorption of inadequately digested nutritive proteins, usually as the result of some intestinal disturbance. But urticaria in animals can also be caused by drugs (iodides, bromides), by metabolites of parasites, by an unbalanced diet containing too much meat, and so on. Chelle²⁷³² describes this condition following spasms of the udder, and believes that it may be explained by retention of milk with resorption of casein, to which the animal becomes allergized. This view is supported by Michaelis and Rona's experiments on suckling bitches: in them, hives were caused by injections of casein, while no reactions could be elicited in male dogs. Schindella reported the case of a bitch that regularly suffered from urticaria when she was in estrus. This case might well be regarded as one of endog-

* ALEXANDER, H. L. *Ibid.* 2: 164, 1931.

† In this type, the cutaneous reactions are confined to the skin sites coming into direct contact with the physical excitant.

‡ In the reflex type, the reactions are not confined to the exposed sites, but also appear in remote parts of the body.

⁷⁷² HELLER, J. Die Klinik der wichtigsten Tierdermatosen. In *Handb. f. Haut u. Geschlechtskr.*, vol. 14, pt. 1, 1930.

²⁷³² CHELLE, Rev. *vél.* 32: 11, 1930.

enous allergy in addition to cutaneous wheals, swelling of the conjunctivae and of the nasal, buccal, esophageal, vaginal, and rectal mucosa has also been observed in animals. Albrecht mentions urinary retention in oxen with urticaria—probably due to edema of the mucosa of the urethra. Finally, hives are not rarely seen in horses injected with foreign proteins for the purpose of preparing immune serums (Fig. 355).



FIG. 355 URTICARIA IN HORSE DUE TO INJECTION OF FOREIGN SERUM

(Courtesy Dr. F. Gerlach)

D. ANGIONEUROTIC EDEMA

Angioneurotic edema is closely related to urticaria, and has indeed been considered by many authors to be a special form of the latter rather than a separate disease. It is true, of course, that angioneurotic edema often appears simultaneously or alternately with hives. However, in view of its distinctive clinical features, including the morphology of its lesions (a white nonpitting edema not accompanied by pruritus), its favorite localization on the face, and the suddenness of its appearance or disappearance, the condition unquestionably merits consideration as an independent entity.

Quincke, in 1882, first described this clinical picture and termed it "acute circumscribed cutaneous edema", after forty years of intensive investigation, the same author published a comprehensive report⁷⁹¹ on the condition. The typical form of the disease is characterized by a sudden attack of one or several circumscribed, usually pale swellings in the subcutis,

without appreciable subjective symptoms. However, the clinical picture often varies considerably from case to case, depending on differences in site and number of the eruptions, intensity of the condition, duration of the attacks, and intervals between them.

The localization of angioneurotic edema is usually on the face (Fig. 356) particularly on the eyelids (Fig. 357) and lips (Fig. 358), however, any other skin area can be affected



FIG. 356 ANGIONEUROTIC EDEMA OF ENTIRE FACE DUE TO HYPERSENSITIVENESS TO STRAWBERRIES

Severe attacks of angioneurotic edema are also characterized by a marked decrease in the excretion of urine—followed, however, by a transitory polyuria after the attack has subsided.

Most to be feared is involvement of the mucosa, above all in the larynx, where the edema can assume such proportions that tracheotomy is frequently necessary. Moreover, in the event that an injection of epinephrine does not bring immediate relief, this operation must often be undertaken without delay, for the literature contains numerous reports of deaths due to suffocation when tracheotomy was not promptly performed. Thus Koening,⁷⁹² in 1924, listed 170 cases in

⁷⁹¹ QUINCKE, H. *Med. Klin.* 17: 675, 1921.

⁷⁹² KOENIG, P. *Folia oto-laryng.*, pt. 1, Orig. 13: 76, 1924.

the literature of which no less than 20 per cent terminated fatally despite tracheotomy. Furthermore, Wason, Hlaváček, and others have since reported additional instances of fatal angioneurotic edema, one case being that of an infant 14 months old in whom the attack followed ingestion of a glass of milk.

of laryngeal edema. Hanhart²⁷⁹⁹ observed this condition in three generations of a family, with fatal outcome in 4 members, and Fineman²⁸⁰⁰ in 6 members in four generations, with one death. It is interesting to note that the edema involves not merely the entire mucous membrane, including the vocal cords, but al-



FIG. 357 ANGIONEUROTIC EDEMA OF PERIORBITAL AND PERIORAL TISSUES AFTER INGESTION OF SARDINES



FIG. 358 SEVERE ANGIONEUROTIC EDEMA OF UPPER LIP IN PATIENT HYPERSENSITIVE TO ACETYL-SALICYLIC ACID (ASPIRIN)

It must be mentioned here that angioneurotic edema, especially of the larynx, is not uncommonly—in fact, with striking frequency—observed to run in families. Osler,²⁷⁹⁶ for one, reported on occurrence of the condition in five generations of a family. Among 80 members in three generations of one family, Ensor²⁷⁹⁷ listed 33 cases of laryngeal edema, 12 of them fatal. Crowder and Crowder²⁷⁹⁸ saw 28 cases representing five generations; 15 of these persons died of suffocation as the result

according to Griffith's microscopic studies, the abductor muscles of the cords, as a result, widening of the opening between the vocal folds during inhalation is prevented.

Edematous states of the other mucous membranes are less dangerous, although involvement of the tongue, soft palate, uvula, and pharyngeal cavity can create difficulty in swallowing and breathing, gravely alarming the patient.

An interesting clinical picture is produced by obstruction of the parotid duct from allergic

²⁷⁹⁶ OSLER, W. *Am J M Sc* 127: 751, 1904

²⁷⁹⁷ ENSOR. *Guy's Hosp Rep* 38: 111, 1904

²⁷⁹⁸ CROWDER, J. R., and CROWDER, T. R. *Arch Int. Med* 20: 840, 1917

²⁷⁹⁹ HANHART, E. in Berger, W., and Hansen, K. (ed.) *Allergie, Leipzig, Thieme, 1940*

²⁸⁰⁰ FINEMAN, A. H. *Ann Int Med* 14: 916, 1940

edema (Pearson²⁸⁹¹) This results in bilateral swelling of the parotid glands in association with angioneurotic edema elsewhere, or with other manifestations of hypersensitiveness In the parotid secretion, as well as in a mucous plug expressed from the duct Hansel²⁸⁹² found a large number of eosinophils

Swelling of the nasal mucosa can produce symptoms simulating 'lead colds', involvement of the conjunctivae causes profuse lachrymation Moreover, similar swellings can also affect the mucosa of the bronchi and of the gastro intestinal and urogenital tracts In addition, the deeper layers of connective tissue, including the periosteum the tendon sheaths, and even the connective tissue of the nerves and of the muscles may be involved The condition can thus provoke the greatest variety of manifestations in the organs named These symptoms are discussed in some detail in relevant sections

It must not be forgotten, however, that symptoms such as coryza, asthma, pulmonary edema, vomiting, diarrhea, colic, arthropathy, and the like, may be regarded as resulting from an angioneurotic process only when they accompany or appear alternately with characteristic manifestations on the skin or visible mucosa—provided also that the given symptoms make their appearance abruptly and then disappear quite suddenly

Cole and Korn²⁴⁴⁸ consider Loeffler's syndrome of transient infiltration of the lungs as presumably due to angioneurotic edema Their own case of bronchopneumonia—verified by X ray—in a child with recurrent edema and an eosinophilia of 54 to 84 per cent, suggests that perhaps other instances of pulmonary involvement in allergies, simulating bronchopneumonia, may also be due to the same mechanism A similar view was expressed by Vaughan and Hawke²⁴⁴⁷

Observations by Schorer²⁵⁸⁰ may be of interest here A woman of 55 years was obliged to keep three changes of clothing of different sizes at hand all the time because of frequent fluctuations in the circumference of her waist A young woman of 21 years presented the phenomenon of alternate increase and decrease in the size of her breasts, which, while

ordinarily pendulous became swollen and firm during an attack Similar cases were previously reported by Diethlen and Bernoulli

When the attacks of swelling are localized within the cranium, the result is likely to be a headache of the migraine type However, they can also lead to focal cerebral manifestations, such as hemianopsia aphasia, convulsions, even apoplectiform states and somnolence, more commonly, involvement of the cerebral nerves gives rise to paresthesias, palsy, oculomotor disturbances, optic neuritis, and vestibular crises These neurologic manifestations appear sometimes simultaneously, sometimes alternately with the cutaneous manifestations Quincke in his time considered the clinical picture of meningo edematous hemicrania to be attributable to an acute circumscribed edema of the pia with possible involvement of the cerebral cortex Disturbances in the vestibular equilibrium apparatus, on the order of Meniere's syndrome, can also be caused by angioneurotic edema

The shock structure in angioneurotic edema is generally considered to constitute the capillaries of the subcutaneous and submucous tissues Pick assumes that the circumscribed swellings are produced by spasm of the venous capillaries of the skin or mucous membrane The extremely transitory nature of the edema and the rapid return to normal might well be explained by the fact that the venous spasm ceases just as abruptly as it commences Occasionally, however, repeated involvement of one skin site can cause permanent damage in the form of thickening of the skin (pachyderma), similarly, repeated angioneurotic changes in certain portions of the brain can result in persistent disturbances of the brain centers located there Thus, in a case with thickening and redness of the skin of the left hand, resulting from repeated attacks of acute angioneurotic edema, Olario²⁵⁰³ observed unusual episodes of loss of consciousness along with disturbances of the vestibular apparatus These Olario interpreted as sequelae to the recurrent angioneurotic edema in the brain, just as the thickening of the skin of the hand was the result of repeated swellings there

²⁸⁹¹ PEARSON R S B Arch Dis Child hood 10 363 1935

²⁸⁹² HANSEL F K Laryngoscope 51 221 1941

²⁵⁰³ OLARIO T Klin Wchnschr 12 1185, 1933

As to the question of etiology, it must be stressed that every case of angioneurotic edema is by no means of allergic origin. In this respect, the condition is comparable to urticaria, and the reader is therefore referred to the section on the etiology and pathogenesis of the latter (p. 739). In some cases, it will be found that angioneurotic edema can be primarily caused by a number of different internal diseases, including those of the gastrointestinal tract (Fig. 359), liver, and gall-bladder, in others, therapeutic results can be



FIG. 359. ANGIONEUROTIC EDEMA DUE TO INFLAMMATION OF SMALL INTESTINE.

Patient remained free of symptoms as long as he adhered to bland diet.

obtained by control of infectious foci—for example, removal of chronically diseased tonsils, or surgical drainage of infected sinuses (Barber,²⁵²⁴ Urbach). Whether the favorable results are due to the elimination of bacterial antigens or of toxins, is often difficult to decide. However, as Dorst and Hopphan²⁵²⁵ were able to show, a case may safely be re-

garded as one of bacterial-allergic origin when the patient has a strongly positive cutaneous reaction to a test with vaccine, and when the attacks cease after systematic desensitization procedures and without an operation. On the other hand, a cure following removal of the infected organ does not, in itself, constitute proof of an underlying bacterial allergy.

Psychosomatic influences, as well as a peculiar predisposition of the neurovascular system, certainly have great importance. In this connection, Wilder's description of the edema appearing as a result of posthypnotic suggestion (Figs. 14, 15) may be cited.

However, numerous cases of angioneurotic edema have unquestionably been proved to be of allergic origin. Thus, Turrettini reported an instance in which the condition regularly appeared following ingestion of small quantities of bread or of other foods containing flour. Lesné and Lévy described a case due to raw horse meat, De Besche, to gooseberry marmalade, Urbach, cases due to strawberries, sardines, and pork, respectively, Kofler, and also Champeau, causation by iodine: Siebermann and Hornicek, by antipyrine, and Pollard, by arsphenamine. Many other comparable examples could be listed, including the interesting observation by Frank¹¹⁰⁸ of laryngeal edema due to chewing gum.

Inhalant allergens are also capable of eliciting these swellings. Here it must be assumed that the causative substances are resorbed by the mucous membranes of the upper respiratory passages. Silbert¹⁷⁹⁶ reported a case due to tobacco hypersensitiveness. Morawitz observed a case in which the edema was evoked by smoking, however, in this instance the allergen appeared to be not the nicotine, but certain pyridines formed as by-products of the combustion of cigarette paper.

In some rare instances, the edema has been found to be evoked by mere epidermal or mucosal contact with the allergen. Thus, Vaughan²¹ reported a woman who developed angioneurotic edema of the lips whenever she touched them with any kind of cigarette. In another case—angioneurotic edema of the tongue and hands after eating watermelon—Vaughan observed that the same swelling of

²⁵²⁴ BARBER, H. W. *Brit. J. Dermat.* 35: 207, 1923.

²⁵²⁵ DORST, S. E., and HOPPHAN, E. *J. Lab. & Clin. Med.* 18: 7, 1932.

¹¹⁰⁸ SILBERT, S. *J. A. M. A.* 114: 1412, 1937.

the hands appeared on mere contact with the juice of the watermelon

The treatment of angioneurotic edema is essentially the same as that of urticaria (p 754) with the exception that inasmuch as there is no itching local antipruritic applications are not needed. In addition cold compresses frequently applied appear to alleviate the swelling to some extent

Angioneurotic edema has also been observed in animals. Both van Leeuwen²⁸⁰⁷ and Phillips⁷⁴ reported the condition in dogs following ingestion of pork or fish. Schwyter described a case of fatal edema of the larynx in a cow

E LICHEN URTICATUS

Lichen urticatus is an entity characterized by the presence of numerous intensely pruritic usually excoriated papules with central bloody crusts. They occur principally on the extensor surfaces of the upper extremities with a marked tendency to spare the flexor aspects. In cases of long duration other areas may also be involved particularly the buttocks and the extensor and flexor surfaces of the legs. In infants and small children lentil-sized watery clear vesicles are not infrequently observed; they are usually quite deep in the cutis and located on the soles of the feet (Fig 369)

The opinion has been expressed that lichen urticatus may be regarded as a variant of urticaria. We are strongly inclined to reject this view, however, because of the radical differences in the two clinical pictures. Moreover we consider the argument that the same etiological factors are to a certain extent common to both to be irrelevant in this connection

Lichen urticatus can be caused exogenously and endogenously. It would be a gross error to suppose that all cases—especially in adults—are necessarily of allergic origin. The disease can in fact be brought on by a variety of conditions such as gastro intestinal disturbances (enteritis colitis constipation) chronic cholangitis kidney disease ovarian dysfunction and parasitic infestations. No deductions can be drawn from the clinical picture as to whether or not a given case is of allergic

origin. It is necessary therefore to subject each patient not only to exhaustive general investigation but also to appropriate allergic tests including the environmental test diet trials propeptan diet and the like. Skin tests are of limited value and in cases of nutritive allergy almost invariably useless (Walzer and Grolnick⁸⁰⁸). The outcome of these studies will permit the physician to conclude whether or not the case is attributable to an underlying allergy

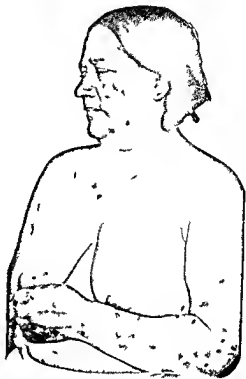


FIG 360 LICHEN URTICATUS ON BASIS OF INTESTINAL PUTREFACTION

For the sake of clarity the manifestations of lichen urticatus in adults and in small children will be discussed separately

In adults lichen urticatus* usually presents the typical picture of excoriated papules on the extensor aspects of the upper extremities (Fig 360) and occasionally also on the back, buttocks and legs (Figs 361-362). There

⁸⁰⁸ *WALZER A and GROLNICK M. *J Allergy* 5:240 1934

*Synonyms: chondropapular urticaria; pustulopapular urticaria

are, moreover, atypical forms of the disease—a fact that does not seem to be sufficiently well known. Some of these forms are sug-

simulate pemphigus vulgaris (FIG. 364). The differential diagnosis is sometimes quite difficult in such cases

Facio²⁹⁹ described a condition, said to be very common in Argentina, which he calls "simple acute prurigo with circumscribed lichenification": the condition is analogous to—if not identical with—what we call lichen

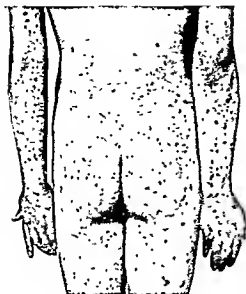


FIG. 361. LICHEN URTICATUS IN ADULT, DUE TO BEEF

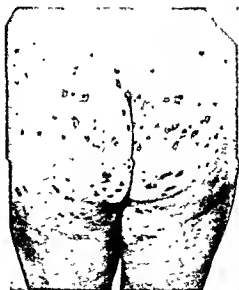


FIG. 362. LICHEN URTICATUS IN ADULT, DUE TO SPICES TAKEN DURING ATTACKS OF COLICUS

At other times, spices were tolerated

gestive of prurigo (FIG. 363), others of dermatitis herpetiformis of Duhring, while in some occasional instances the picture may even



FIG. 363. LICHEN URTICATUS OF LONG STANDING, DUE TO HYPERSENSITIVENESS TO BEEF

urticatus. In the Argentine, the disease is considered to be due, in many instances, to the fact that the shepherds habitually overindulge in alcohol when they go into town, and then also eat food to which they are not accustomed. The condition manifests itself, first, by diarrhea and fever, accompanied by intense itching that attains its maximum within about five or six days; then cutaneous lesions, consisting of numerous lichenified papules, appear. After a few weeks, the dermatosis begins to

regress unless secondary cutaneous manifestations arise and prolong the course of the disease. This example affords an excellent illustration of nutritive allergization as a result of irritation of the intestines by overindulgence in alcohol and might very well *mutatis mutandis*, serve to explain the pathogenesis of the nutritive allergic forms of lichen urticatus in many cases outside of Argentina.

of instances due to exogenous allergic factors other than foods. Appropriate diagnostic



FIG 365 LICHEN URATICUS ON BASIS OF BACTERIAL ALLERGY

Proved by positive reaction to streptococcus vaccine and disappearance of lesions after extirpation of infected tonsils



FIG 366 TYPICAL DISTRIBUTION OF LICHEN URATICUS Caused by egg hypersensitiveness

FIG 364 BILLOUS FORM OF LICHEN URATICUS OF TEN YEARS DURATION CLINICALLY RESEMBLING PEMPHIGUS VULGARIS

Allergens proved to be egg, wheat and pork. Cured by propeptan therapy in eight weeks

In seeking to identify the causative food allergen, it is to be borne in mind that not only animal and vegetable foods but also carbohydrates, fats, acids, and salts must be considered. It should also be remembered that every case of allergic lichen urticatus is not necessarily caused by food. FIGURE 365, for example, shows a case resulting from bacterial allergy arising from infected tonsils. Furthermore, the authors observed a number

methods usually revealed the identity of the allergen

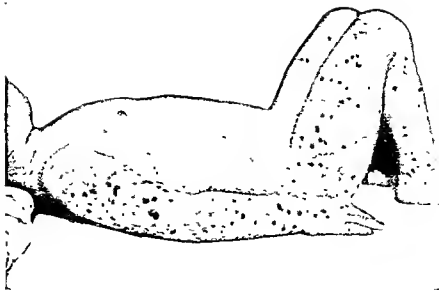


FIG. 367. LICHEN URTICATUS IN CHILD DUE TO WHITE BREAD

Lichen urticatus in infants and small children* is a relatively common disease (FIGS. 366-369). Occasionally, the eruption first appears when the child is being weaned and placed on artificial feedings; more commonly, however, the condition is associated with some gastro-intestinal disease or digestive disturbance. This pathogenesis explains why the condition is almost invariably of nutritive-allergic origin in infants and why it can often be rapidly cured by proper dietetic measures or administration of propeptans. The same holds true, but to a much lesser extent, in small children.

In the majority of children, lichen urticatus is fully cured—spontaneously, in not a few instances—without sequelae after a course lasting from months to one or two years, and characterized by increasingly longer symptom-free intervals. In some cases, however, the recurring attacks increase in severity (FIG. 370), and the condition finally assumes the characteristic picture of Hebra's prurigo: only slightly elevated, intensely pruritic papules, with secondary lichenification and hyperpigmentation of the skin, accompanied by the appearance of so-called prurigo buboes.

The senior author²⁵¹³ had occasion to study 225 cases of lichen urticatus in children of all ages. In all cases in infants and very young children, an underlying nutritive allergy was



FIG. 368. LICHEN URTICATUS DUE TO HYPERSENSITIVENESS TO SPINACH

demonstrable. In those beyond this age, actual elicitation of an attack by administration of a given food (usually milk, egg, veal, or

* Synonyms: *strophulus infantum*, *urticaria chronica infantum*
²⁵¹³ URBACH, E. *Dermat. Ztschr.* 78, 77, 1938

pork) was regularly possible in only 30 cases in these same children withdrawal of the food items served to prevent the appearance of symptoms In 5 additional instances it

ingredients ingested separately elicited no response In 15 cases although it was impossible to identify the nutritive allergens administration of polypropeptans resulted in



FIG 369 LICHEN URTICATUS DUE TO MILK ALLERGY INVOLVING SOLES IN CHILD OF 18 MONTHS

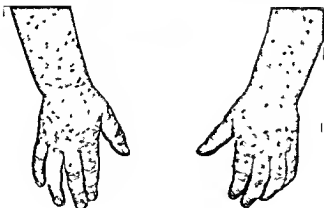


FIG 370 LICHEN URTICATUS DUE TO WHEAT ALLERGY
Resembling prurigo

was found that not one but several foods in combination constituted the causative agents, as follows milk and egg, smoked meat and spinach, potato and apple egg and apple In one child, the symptoms could be evoked only by giving a soup composed of tomatoes lemons, and bouillon cubes, the individual

complete cure According to Bray²⁸¹¹ pork products, fish eggs, potatoes, chocolate, and particularly fats are usually the exciting factors

In children past the age of 3, it was found

²⁸¹¹ BRAY G W Brit J Child Dis 34 180 1933

that exogenous factors played a dominant part in the etiology. It is true that animal and vegetable foods as well as carbohydrates (Weigert,²⁵¹² Mathieu,²⁵¹³ Urbach²⁵¹⁰) are operative in a certain percentage of cases, but in the great majority, day and night trials, as well as skin tests, will reveal some environmental allergen as the causative agent. Lastly, one must not fail to consider the possibility of endogenous allergens of a bacterial nature, resulting from tonsillitis, otitis, or respiratory infections, and parasitic infestations. Nor should the fact be overlooked that fever, gastro-intestinal disturbances, and the like can provoke recurrences of lichen urticatus after a long period of freedom from symptoms.

As stressed above, lichen urticatus is by no means necessarily of allergic origin. According to Pillsbury and Sternberg,²⁵¹⁴ the condition may sometimes be related to a calcium deficiency, as a result of precipitation of absorbable calcium by ovalates in the foods; such cases may be cured by parathormone therapy. In occasional instances, external causes such as insect bites, especially of fleas and bedbugs, have been identified as the cause.

The therapeutic approach consists entirely in the discovery and elimination of the causal agent; when the condition is found to be due to some exogenous or nutritive allergen, the therapeutic measures outlined on page 754 are to be instituted.

F. PRURIGO

In connection with the discussion of lichen urticatus, the relatively uncommon but none the less important entity known as prurigo merits consideration. Distinction is made between two forms of the disease which differ only in degree: a severe type, prurigo ferox of Hebra, and a comparatively mild type, prurigo mitis.

Clinically, the disease is characterized by the sudden appearance of pinhead- to lentil-sized skin-colored papules. From the onset of the condition, the patient suffers from extraordinarily intense itching that may be constant or in the form of recurring attacks. The

parts most likely to be affected are the extremities—the upper more commonly than the lower (FIG. 372). As a result of the uncontrollable scratching, the skin becomes thickened, at the same time the lymph nodes undergo a characteristic indolent swelling, leading to the so-called prurigo buboes (FIG. 371) in the inguinal, epitrochlear, and axillary regions.

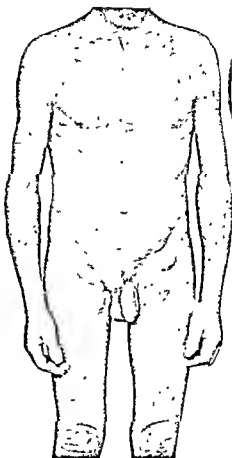


FIG. 371 PRURIGO OF HEBRA, WITH HUCK BUBOES

Since the cause is determined only in occasional instances, the disease goes on for many years, with some remissions; sometimes a cure occurs spontaneously at puberty.

The pathogenesis of this disease has not as yet been definitely determined. Kerl²⁵¹⁵ is of the opinion that there is a close pathogenetic relationship between prurigo and lichen urticatus. On the basis of relatively extensive

²⁵¹² WEIGERT, R. *Monatsschr. f. Kinderh.* 25: 669, 1923.

²⁵¹³ MATHIEU. *Bull. Soc. de pediatrie de Paris* 26: 519, 1928.

²⁵¹⁴ PILLSBURY, D. M., and STERNBERG, T. H. *Am. J. Dis. Child.* 53: 1209, 1937.

²⁵¹⁵ KERL, W. *Dermat. Wchnschr.* 100: 391, 1935.

clinical and experimental experience with this condition the present writers are inclined to agree with this view. It is not uncommon to see a direct transition from a refractory lichen urticatus in early life to prurigo as the individual grows older.

The pathogenesis is not uniform. Certainly it is not always attributable to allergy. However it is true that in the majority of the

and Urbach²⁰ employing the so called day and night tests succeeded in demonstrating the etiologic significance of exogenous agents. It is an old clinical observation that a few days hospitalization without any treatment whatsoever will frequently render a patient with prurigo symptom free (Figs 372-373); even the prurigo buboes will disappear spontaneously. Moreover it has been commonly

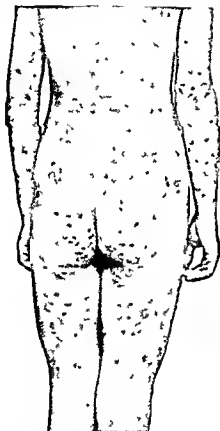


FIG 372 HIEBER'S PRURIGO OF TEN AND A HALF YEARS' DURATION IN 11 YEAR OLD GIRL

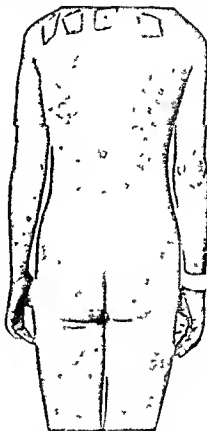


FIG 373 SAME PATIENT AFTER FIVE DAYS IN HOSPITAL WITHOUT ANY THERAPY

Illustrating importance of environmental factors in this disease

cases in the writers' own experience it was possible to demonstrate the presence either of an exogenous or of a nutritive allergy.

It was J. Jadassohn who some forty years ago first called attention to the importance of environmental factors in the causation of some cases of prurigo. This observation was to all appearances totally overlooked until simultaneously and independently Hallam²¹ and

observed that shortly after the patient's discharge—usually within a few days but sometimes on the very night of his return home—the same subjective or objective cutaneous manifestations recur.

The senior author had occasion to observe one case of severe prurigo in which the existence of an exogenous allergy became vividly apparent. Since there was reason to suspect

²¹ HALLAM R. B. *J. Dermat.* 44: 117, 1932

²⁰ URBACH E. *Wien klin. Wochschr.* 45: 762, 1932

an allergy to straw, the patient was instructed to spend the night away from his home, but to be sure to sleep on a straw mattress wherever he went. A married couple offered him the hospitality of their double bed. In order not to disturb his hosts, the patient was careful to sleep on his right side all night long. FIGURE 374 clearly shows the result—prurigo papules localized almost exclusively on the right side of his back.

day and night tests would naturally be of no value.

Occasionally, environmental tests will reveal that the causative agent is somehow associated with the patient's home, but despite all efforts, the actual identity of the excitant will still remain unknown. In such cases, the patient should, as a last resort, be advised to move. By recommending this drastic step, the senior author^{25, 27} succeeded in bringing

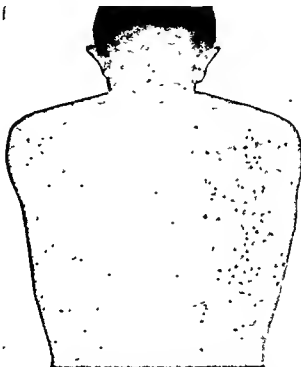


FIG. 374. PAPULAR REACTION TO STRAW IN PATIENT WITH PRURIGO DUE TO HYPERSENSITIVENESS TO STRAW. Unilateral localization is explained in text.

In another case, it was possible to demonstrate hypersensitiveness to woolen blankets.

It should be noted, however, that the search for the excitant should by no means be limited to inhalant and contactant factors. Thus, the senior author observed a girl of 15 years whose prurigo was found to be due to an extreme hypersensitiveness to milk, propeptan treatment over a period of three weeks cured the condition. Moreover, not only protein foods, but also salts, acids, spices, and the like must be considered as potential allergens, and appropriate diet trials should therefore be instituted. Bacterial or endogenous allergens may, of course, be the excitants in occasional instances. In cases of this kind, the

about a speedy and lasting cure in a family afflicted with prurigo. Four children between the ages of 10 and 21 years suffered either from typical prurigo or from severe lichen urticatus for many years, until their residence was changed. A follow up revealed no recurrence during an observation period of eight years.

G. PRURITUS

It is a generally known fact that many allergic diseases, whether characterized by systemic or local manifestations, are accompanied by pruritus, in some instances, the itching appears only at the onset, in others it persists more or less throughout the entire course. Moreover, this applies not only to

the allergic skin diseases (urticaria dermatitis neurodermatitis prurigo and lichen urticatus) in which pruritus is sometimes the outstanding symptom but also to allergic conditions involving the eyes ears nose and other organs. It will also be found true in systemic conditions such as serum disease and anaphylaxis. Furthermore as Doerr pointed out more or less intense itching not infrequently is the first evidence of an allergic reaction and if the attack is abortive may even be the only sign. In other cases there are paroxysmal attacks of itching that are often confined to one site (e.g. anus vulva) and that as will be shown below may be fundamentally at

suspected cause and consistently reappears after deliberate exposure to it this demonstrates that the condition is the expression of an allergic hypersensitiveness to the given agent. In such instances the allergen is usually found to be a food or drug but may also be a contactant such as feathers (Fig 376)

Similarly generalized or localized pruritus can occasionally be proved to be due to hypersensitiveness to a drug. Sokolowsky reported such a case in which cinchophen was found to be the allergenic agent and Fuerbringer reported a case due to hypersensitiveness to carbromal. Many similar observations could

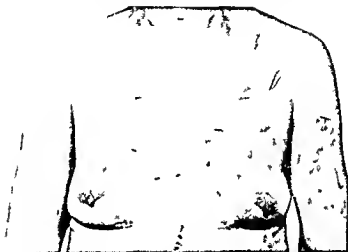


FIG 375 ALLERGIC PRURITUS DUE TO HYPERSENSITIVENESS TO PORK

tributable to a specific allergy. FIGURE 375 gives some idea of the degree of intensity attained by the pruritus; the parallel scratch marks over the entire body are characteristic.

Needless to say pruritus may be caused by a great variety of nonallergic factors. Mention of only a few examples would include the disturbed metabolism in diabetes and gout, leucemia and lymphogranulomatosis, liver and gallbladder diseases, gastrointestinal disorders, intestinal parasites, endocrine dysfunctions and toxic states.

On the other hand, cases are also encountered in which the pruritus is unquestionably of allergic origin. The only means by which the diagnosis can properly be made are elimination and re-exposure tests, i.e. if the pruritus promptly ceases on avoidance of the

be cited. One special example of the localized form allergic pruritus and due to foods, drugs and other agents was discussed on page 678.

The question as to whether pruritus following the use of coffee, tea, alcohol and tobacco is to be regarded as an allergic manifestation or as an expression of irritability of the central or peripheral nervous system resulting in dilatation of the cutaneous blood vessels must be decided in each case on the basis of appropriate tests. It should be noted however that according to the observations of Bulkley, Jessner and others, stimulants may sometimes constitute the sole cause of pruritus ani and pruritus vulvae.

Pruritus not infrequently occurs in patients with focal or parasitic infestations, malignant tumors and constipation or other gastro-

intestinal disturbances, as well as in pregnancy. In any of those conditions it is difficult to decide whether the pruritus is allergic or toxic in character. Many a case of this kind will be found to be unquestionably due to toxins. On the other hand, it is now becoming increasingly apparent that the diseases and disturbances mentioned can bring about the formation of auto- or hetero-endogenous allergens that allergize the organism, and that the

initial annual onset (particularly on the extremities) on one of the first cold days in the autumn, and does not disappear until spring; during the winter months, the severity of the pruritus fluctuates in direct ratio to the intensity of the cold. Occasionally, the pruritus develops into a prurigo hiemalis. However, the problem of whether the cold alone is responsible for pruritus hiemalis must be answered by appropriate tests in each case, since quite frequently the itching is actually caused by woolen clothing or underwear commonly worn during cold weather. According to Sells, pruritus hiemalis is not related to allergic hypersensitiveness to cold, he considers the condition to be the expression of a paradox sensory perception.

Hutchinson has described a condition analogous to pruritus hiemalis—namely, pruritus aestivalis, which may well be regarded as the best symptom of a specific light hypersensitiveness known as prurigo aestivalis (see p. 421). Here again it is necessary, of course, to rule out excessive sweating and other chemical or mechanical irritants as the possible cause.

There is also a form of itching due to the influence of heat—an abortive form of heat urticaria. The name "cholinergic itching" was suggested by Nørlund²³⁴ for that form which occurs in frequent, brief, explosive attacks without whealing of the skin, following exposure to heat, exercise, or emotional stress, and reproducible at will in susceptible individuals by injections of acetylcholine or pilocarpine. Unlike "cholinergic urticaria," it is thought probably to result from a direct action of the choline substances on the cholinergic nerves of the skin and thereby produce itching in some unexplained way.

Finally, the importance of psychic factors cannot be overemphasized. While in some cases the itching is solely an expression of emotional imbalance, in others it is due to psychosomatic influences, particularly in the menopause.

In view of the fact that pruritus can be due to a great variety of causes, it is impossible to recommend one general therapeutic approach. Every case must be subjected to painstaking



FIG 376 PRURITUS AND EXCORIATIONS OF SCALP, DUE TO HYPERSENSITIVENESS TO FEATHER PILLOWS

resultant antigen-antibody reaction can produce pruritus as well as other allergic phenomena. We do not as yet possess a method for differentiating between a toxic and an allergic pathomechanism in such cases, partly because we are still unable to isolate the antigenic substance chemically, and partly because the primary shock tissue is often not the skin.

Pruritus hiemalis, a condition basically due to cold, must also be considered here. Duhring first called attention to the fact that in many persons the itching regularly has its

²³⁴N. NØRLUND, R. Arch. Dermat. & Syph. 50:21, 1944

internal investigation with the object of determining whether there is any evidence of a metabolic imbalance, hematopoietic disease, gastro intestinal disorder, focal infection, parasitic infestation, endocrine dysfunction, or, above all, disturbing psychic influence, any of which might be the fundamental cause. If no such condition is found, one next considers, especially in cases with personal or family histories of allergy, the possibility of some allergic or pathergic hypersensitiveness. It is then necessary to carry out all conceivable studies, including elimination, environmental, and skin tests (with bacterial preparations), as well as those for physical allergy, in an effort to determine the exact nature of the hypersensitiveness, if any. When none of these approaches clarifies the pathogenesis, it is necessary to resort to nonspecific therapeutic methods, of which the most promising is roentgen irradiation. In the case of senile pruritus, the treatment originally introduced by Luthlen, consisting of a series of injections of sodium silicate (1 cc of a 1 per cent solution), was often found by the senior author to be helpful. In addition, a salt poor diet may be well worth trying.

H DERMATITIS HERPETIFORMIS (DUHRING)

At the very outset, we wish to state that, on the basis of the senior author's experimental investigations,²⁸¹⁹ we are of the opinion that dermatitis herpetiformis and pemphigus vulgaris are to be regarded as virus infections.

Nevertheless, this group of diseases is accorded at least brief consideration here for two reasons: first, because Darier and Tzanck concluded that dermatitis herpetiformis is, in effect, an expression of hypersensitiveness to iodine, basing their opinion on the well known fact that administration of iodine, either by epidermal test or by mouth, causes vesiculation in these patients. Moreover, as additional evidence, they called attention to the marked eosinophilia usually observed in this disease. On the other hand, Lehner and Rajka had previously expressed the opinion that the hypersensitiveness to iodine is merely

the result of sensitization arising coincidentally with infection by the presumed virus.

Against these concepts may be cited the following facts: (1) In dermatitis herpetiformis, there is not an isolated hypersensitiveness to iodine, but rather a sensitivity to the entire halogen group: iodine (J. Jadassohn), bromine (Jessner and Hoffmann), and chlorine (Urbach). (2) The senior writer has demonstrated that the iodine hypersensitiveness is not pathognomonic of dermatitis herpetiformis, but is actually present in almost all skin diseases characterized by blister formation, such as erythema multiforme, lichen ruber pemphigoides acute and subacute dermatitis, and mycotic infections provided these are accompanied by vesiculation.

A number of authors—including Pasini and Bizzozero—regard dermatitis herpetiformis as a toxic symptom complex. Moreover, it may be said that dermatitis herpetiformis is not an entity characterized by a sharply defined clinical picture, but is marked by more or less simultaneous occurrence of erythematous, papular, vesicular, or bullous lesions that exhibit a tendency toward grouping, and are as a rule accompanied by intense pruritus. It is obvious, therefore, that allergic or toxic skin conditions may readily simulate this disease. The senior writer has had occasion to observe many cases that, at first glance, suggested the diagnosis of dermatitis herpetiformis, but in which thorough investigation revealed an infectious, toxic, or allergic origin. Thus, the senior author⁴⁶³ reported a case in which extraction of an infected tooth resulted in complete freedom from symptoms (Fig. 377), subsequently, an injection of autogenous vaccine prepared from the infected root of the tooth promptly evoked a short lived vesicular outbreak.

Callaway and Sternberg²⁸⁷⁰ reported a case in which the cutaneous manifestations were apparently due to hypersensitiveness of the skin to pneumococci from a bronchiectasis, as indicated by positive intradermal and patch tests with an autogenous vaccine. Desensitization therapy with the vaccine was instrumental in producing relief from the cutaneous symptoms. This is therefore an instance of

bacterial allergy simulating dermatitis herpetiformis. Lastly, the writers have seen at least 4 cases in which exogenous allergens elicited this same disease picture. In all of them, a complete change of environment afforded complete cure. Sammis^{23,24} described a case of dermatitis herpetiformis following ingestion of eggs, beef, fish, and cheese, while Sutton^{19,25} observed a child whose lesions appeared after drinking cow's milk.

sion of hypersensitiveness to egg and wheat flour; healing was achieved within two months by means of propeptan treatment. A similar case of pemphigus-like skin manifestations as an expression of a nutritive allergy was reported by Gougerot and Blamoutier.^{22,23} Their patient regularly responded to chocolate and champagne with vesicular eruptions, as well as symptoms of a hemoclastic crisis and a marked drop in blood pressure.

I. ERYTHEMA MULTIFORME

Erythema multiforme is an acute exudative disease of the skin characterized by recurrent



FIG. 377. DERMATITIS-HERPETIFORMIS LIKE DERMATOSIS DUE TO DENTAL INFECTION.

Permanently cured after extraction of infected tooth.

Moreover, an allergic dermatosis can occasionally mimic the clinical picture of pemphigus as well as dermatitis herpetiformis. FIGURE 364 shows a patient who for about ten years suffered from bullous eruptions strongly suggesting pemphigus in its clinical appearance. However, closer investigation revealed that this dermatosis was actually an expres-

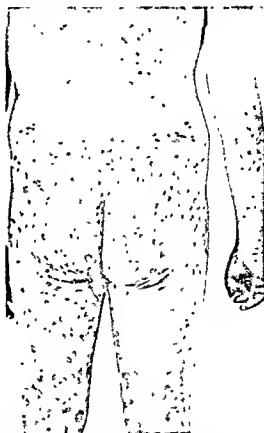


FIG. 378. RECURRENT ERYTHEMA MULTIFORME PROBABLY DUE TO HYPERSENSITIVENESS TO PATHOLOGIC INTESTINAL FLORA, CHIEFLY STREPTOCOCCI.

Injection of 500,000 organisms of stool vaccine resulted in large isomorphic local reaction as well as flare of exanthem.

erythematous or polymorphous symmetrically distributed eruptions on the face and neck,

^{23,24} SAMMIS, F. E. *ibid.* 32: 798, 1935.

^{25,26} SUTTON, R. L. *Am. J. M. Sc.* 140: 725, 1910.

^{22,23} GOUGEROT, H., and BLAMOUTIER. *Arch. dermat. et syph. Hôp. St. Louis* 2: 318, 1930.

and on the dorsal and less commonly the volar surfaces of the hands and feet. The pathogenesis of erythema multiforme is as yet entirely unknown but it is generally regarded as hematogenous in character. Some authors are of the opinion that the condition is caused by either bacterial or toxic emboli. Thus Leipner²⁸² observed an outbreak of erythema multiforme in 30 of 56 boys in a boarding school about eight to ten days after a mild epidemic of coryza.

FIGURE 378 illustrates an erythema multiforme that regularly appeared in a colleague

The senior author²⁸³ has observed that erythema multiforme is very frequently preceded by herpes labialis—the former appearing after an interval of about seven to ten days—and considered it a generalized herpetic exanthem (FIG 379) the question as to whether the condition is to be regarded as allergic in view of the time interval or as a result of hematogenous distribution of the herpes virus cannot as yet be conclusively answered. Similar findings have been reported by Forman and Whitwell²⁸⁴ and Anderson²⁸⁵.



FIG 379 ERYTHEMA MULTIFORME FOLLOWING TEN DAYS AFTER HERPES LABIALIS

of the senior author following attacks of tonsillitis; it was impossible to ascertain whether the skin condition was of infectious, toxic or bacterial allergic origin. Barber²⁸⁶ and Templeton²⁸⁷ hold that erythema multiforme is an allergic reaction to existing foci of infection. In their investigation of a series of cases of recurrent erythema multiforme Barber and Forman²⁸⁷ encountered numerous positive skin reactions to *Streptococcus haemolyticus* and reported satisfactory therapeutic results with vaccines.

In other cases erythema multiforme is to be looked upon as the clinical expression of a drug allergy evoked for example by arsenophenamines, by gold or by phenobarbital.

Furthermore a number of observations have been reported to the effect that this condition appeared after certain foods were eaten. Galloway described a case of erythema multiforme following ingestion of black currants and nuts. Engman as well as Klauder reported reactions to pork. Fordyce to lobster and Touton to shrimps. Whether the manifestations in a given case are truly due to an

²⁸² LEIPNER S. *Dermat. Wechschr.* 101: 1178, 1935.

²⁸³ BARBER H. W. *Guy's Hosp. Rep.* 71: 36, 1921.

²⁸⁴ TEMPLETON H. J. *California & West Med.* 28: 64, 1928.

²⁸⁵ BARBER H. W. and FORMAN L. B. *J. Dermat.* 4: 4, 1933.

²⁸⁶ URRACH E. *Zentralbl. f. Haut u. Geschlechtskr.* 46: 413, 1933; 48: 448, 1934; 57: 12, 1937.

²⁸⁷ FORMAN L. and WHITWELL C. P. B. *Brit. J. Dermat.* 46: 309, 1954.

²⁸⁸ ANDERSON N. P. *Arch. Dermat. & Syph.* 51: 10, 1945.

allergic reaction or constitute an exanthem of alimentary-toxic nature, can be determined only by readministering the same food after the cutaneous manifestations have disappeared: if the same symptoms reappear, the allergic origin is proved.

Lastly, mention might be made here of Gerson's observations²³¹ on himself. Ingestion of blackberries regularly elicited herpes labialis, with subsequent thickening of the labial mucosa. Hoffmann described a similar case: during fifteen years, the herpes of the lips regularly appeared twelve hours after ingestion of pork, and persisted from three to five days.

J. ERYTHEMA NODOSUM

The term erythema nodosum designates an acute condition marked by the appearance of painful reddish-purple subcutaneous nodules or plaques, usually situated over the tibia, but occasionally also on the extensor or flexor surfaces of the thighs, and associated with fever, arthralgia, and malaise. The manifestations as a rule disappear spontaneously after about two to three weeks, without ulceration but with residual pigmentation.

As with erythema multiforme, so too there is a considerable divergence of opinion as to the pathogenesis of erythema nodosum. It cannot be attributed to any one cause, since it is a morphologic rather than an etiologic entity. Therefore, the disease picture may be produced by any number of different agents, such as streptococci, tubercle bacilli, *Bacillus crassus*, fungi, and drugs. In a great many cases it was possible to culture bacteria or fungi from the contents of the nodules, these cases may thus be properly regarded as instances of hematogenous infection. On the other hand, Hellerström²³² and others have observed such eruptions in patients with lymphogranuloma inguinale, appearing after the buboes had been subjected to radiotherapy. They therefore regard the cutaneous manifestations as the reaction of a highly allergic skin to hematogenously distributed

antigen ("id" phenomenon). Skiöld²³³ shares the general concept that this disease, as well as erythema multiforme, is an allergic phenomenon due to multiple etiologic factors. Perry²³⁴ emphasizes the point that the causative agents give rise to the syndrome only in patients constitutionally predisposed and points to the frequency with which other members of the family suffer from the condition as evidence that the diathesis is partly inherited.

Particularly controversial is the question as to whether or not erythema nodosum is of tuberculous origin. While it is true that some cases are certainly of this etiology (Stokes,²³⁵ Ramel,²³⁶ Gray,²³⁷ Wallgren²³⁸), Wallgren²³⁸ holds that, in childhood at any rate, erythema nodosum is not directly caused by the tubercle bacillus, but represents a parallergic phenomenon in the course of the specific infection. He bases his concept on the fact that the condition appears either when the specific allergy resulting from the tuberculous infection first arises (generally from three and a half to seven weeks after onset of the disease) or later in the course of the tuberculosis, but always at the time of some major fluctuation in the tuberculous allergy. Perry²³⁴ found the percentage of positive Mantoux tuberculin reactions in patients with erythema nodosum under the age of 15 years to be approximately three times that in those over that age. Montgomery et al.²³⁹ believe that the chronic forms which have been attributed to tuberculosis are actually examples of nonulcerative types of erythema induratum or types of nodular vasculitis. They hold that the disease tends to be associated with streptococcal infection, including foci of infection in the teeth and tonsils.

Moreover, according to Moro, erythema nodosum is to be regarded as a parallergic reaction when it starts—as it has frequently been observed to do—some seven to ten days

²³¹ GERSON, M. *Diättherapie der Lungentuberkulose*. Vienna Deutsche, 1934.

²³² HELLERSTRÖM, S. *discussion to Souck, C. E.* *Acta dermat*

²³³ SKIÖLD, N. *Acta med Scandinav.*, suppl 1943.

²³⁴ PERRY, C. B. *Brit M J* 2, 543, 1944.

²³⁵ STOKES, J. H. *Arch Dermat & Syph* 3, 29, 1921.

²³⁶ RAMEL, E. *Boll. Soc. franc. de dermat. et syph.* 45, 1245, 1938.

²³⁷ GRAY, W. D. *Brit M J* 2, 286, 1945.

²³⁸ WALLGREN, A. *Ztschr. f. Kinderh.* 43, 343, 1927.

²³⁹ MONTGOMERY, H., O'LEARY, P. A., and BARKER, N. W. *J.*

A M A 128, 335, 1945.

²³² GERSON, M. *Diättherapie der Lungentuberkulose*. Vienna Deutsche, 1934.

²³³ HELLERSTRÖM, S. *discussion to Souck, C. E.* *Acta dermat venereol* 20, 539, 1939.

days after an attack of tonsillitis the onset of scarlet fever or vaccination

Another disputed question is whether cases of erythema nodosum in adults are to be considered as due to the same etiologic mechanism as are those in children

Lastly the literature contains numerous reports of cases in which the nodule formation was demonstrably due to drug allergy (salicylates antipyrine bromides) The senior author has observed a similar instance—a disseminated nodular eruption due to phenolphthalein

K. EOSINOPHILIC ERYTHREDEMA

An epidemic occurrence of cases of eosinophilic erythredema in Palestine was reported by Klopstock and Steinetz²⁵⁴⁰ and Leffkowitz and Sukienik²⁵⁴¹ The disease usually starts with severe itching or occasionally only with pain This is associated with swelling and infiltrations of the skin and mucous membranes accompanied by local heat and redness and occasionally taking the form of lymphangitis The lesions are transient usually subsiding in two or three days but may appear elsewhere or be migratory in character involving large areas of the body at different times There is eosinophilia of the blood sternal bone marrow and tissues and frequently leukocytosis After the acute manifestations subside subcutaneous nodules are sometimes found Although the etiology is unknown the condition is believed to be an allergic phenomenon

L. LUPUS ERYTHEMATOSUS

The discussion here will be confined to the possibility that some cases of lupus erythematosus may be based on or related to light hypersensitiveness or that they may represent some other as yet poorly understood form of hypersensitiveness

It is a common observation that the onset of the disease or its exacerbations follow exposure to sunlight or ultraviolet irradiation Moreover porphyrin was found by Ludy and Corson²⁵⁴² in the urine of some of their

patients while in other cases (Fig 380) porphyrin is present only in the stool (Urbach and Thomas²⁵⁴³) However the relation of lupus erythematosus to light is far from being understood There is certainly not sufficient evidence to conclude that this disease is basically due to a disturbance of porphyrin metabolism as is hydroa aestivale There is



FIG 380 LUPUS ERYTHEMATOSUS DISSEMINATUS IN EXACERBATION AFTER EXPOSURE TO SUNLIGHT

Porphyrin as present only in stool

support for this statement in the facts that a certain percentage of patients with lupus erythematosus may be exposed to sunlight or ultraviolet light without any deleterious effects and that no porphyrin can be detected in the blood urine or stool There is reason to assume that in some cases porphyrinemia and porphyrinuria are dependent on impairment of the function of the liver which normally

²⁵⁴⁰ KLOPSTOCK A and STEINETZ H Harefuah 28 117 1949

²⁵⁴¹ LEFFKOWITZ M and SUKIENIK S ibid 28 120 1949

²⁵⁴² LUDY J B and CORSON E F Arch Dermat & Syph 37 403 1938

²⁵⁴³ URBACH E and THOMAS C C Br J Dermat 51 343 1959

destroys this substance. Finally, in instances of isolated stercoporphyria, an abnormal intestinal flora should be thought of. Pertinent to this is the observation of the senior author that from the stools of two such patients, strains of *Bacillus coli* were cultured that had the capacity of forming porphyrin *in vitro* under the influence of ultraviolet irradiation.

There is also the entirely independent possibility that a bacterial allergy may be the underlying mechanism and that the irradiation is the precipitating factor. Streptococci and tubercle bacilli particularly have been implicated in this regard.

According to Fox,²³⁴ the clinical and pathologic features of disseminate lupus erythematosus present some aspects suggesting that this disease may be primarily a manifestation of hypersensitiveness. Moreover, by analogy, the pathologic lesions in certain cases resemble those of periarteritis nodosa, which, in view of recent observations (see chap XXIX), may be considered to have a fairly well established allergic basis. Fox described a case in which there was presumptive evidence that a foreign protein, antitetanic (horse) serum, was the initiating factor and perhaps the actual cause of a disease process clinically and pathologically typical of disseminate lupus erythematosus. Klemperer, Pollack, and Baehr²³⁵ characterized this condition as a "diffuse collagen disease" and pointed out that the manifold alterations of the disease process are probably caused by a basic injury primarily localized in the connective tissue of the blood vessels and not in the epithelium as believed by other authors. The basic lesion is a fibrinoid degeneration of the collagen. A process essentially similar but with varied anatomic distribution is thought to occur in rheumatic fever, periarteritis nodosa, and thromboangiitis obliterans (Roessle²³⁶), scleroderma (Masugi and Yae-Shu²³⁷), dermatomyositis, and Libman-Sachs syndrome. Klemperer and his associates²³⁵ were aware of the fact that

fibrinoid degeneration had been described as an expression of a hypersensitive state by Gerlach.²³⁸ Fox also stresses the similarity in general symptomatology between disseminate lupus erythematosus and serum sickness, and suggests the possibility that the former, like periarteritis nodosa, may eventually prove to be a pattern of reaction to a variety of antigens in hypersensitive persons. One such antigen may be related to the action of actinic rays on the sensitized body.



FIG 38t LIGHT DERMATOSIS RESEMBLING LUPUS ERYTHEMATOSUS

Stokes, Beerman, and Ingraham,²³⁹ in a thorough analysis, consider disseminate lupus erythematosus as an expression of vascular allergy based on an infection-allergic mechanism, in contrast to chronic discoid lupus erythematosus which seems to depend on allergic (hyperergic) follicular inflammation, closely allied if not identical with the "id" concept. The infectious allergy of the disseminated form has its origin most often in streptococcal infections, possibly in tuberculous and other infectious diseases. The theory of vascular allergy as the underlying basis

²³⁴ FOX, R. A. Arch Path 36: 311, 1933

²³⁵ KLEMPERER, P., POLLACK, A. D., and BAHR, G. J. A. M. A. 119: 331, 1942

²³⁶ ROESSELE, R. Klin Wchnschr 15: 509, 1936

²³⁷ MASUGI, M., and YAE-SHU. Arch f path Anat 302: 39, 1938.

²³⁸ KLEMPERER, P., POLLACK, A. D., and BAHR, G. Arch Path. 32: 569, 1941

²³⁹ GERLACH, W. Virchows Arch f path Anat 247, 294, 1923

²⁴⁰ STOKES, J. H., BEERMAN, H., and INGRAHAM, N. R. Am J. M. Sc 207: 549, 1944

may explain the multiform nature of the lesions and the fact that the manifestations are either preponderantly local and cutaneous or preponderantly systemic. In support of a vasculo-allergic mechanism can be cited the following observations: the recognized danger of stirring up a focus of infection (especially dental) the experiences with sulfonamides which appear to help in some cases by controlling an infectious focus or to make others worse by activating or stirring up a focal infection (Barber²⁵⁰ Rubin²⁵¹) the high incidence of photosensitivity the almost invariable occurrence of leucopenia suggestive of an allergic assault on the bone marrow and the extreme even fatal reactivity of disseminated types to tuberculo-toxin.

A possible relationship to the Sanarelli-Schwartzmann phenomenon has also been suggested.

Another explanation of this disease was advanced by Jausion²⁵² under the concept of photobiotropism. This connotes that under the influence of light certain cutaneous manifestations that would otherwise remain latent become manifest.

Finally it should be borne in mind that the clinical picture of lupus erythematosus may be closely simulated by simple light hypersensitivity (FIG 381). The differentiation can readily be made by having the patient wear a mask for two or three days. A light dermatosis will nearly entirely disappear in this time while in erythematosus lupus there will at best be only slight improvement.

M PURPURA

As is well known purpuric disorders may result from (1) coagulation defects (from deficiency of fibrinogen prothrombin or calcium) (2) diminution of the blood platelets owing to excessive destruction by the spleen as in idiopathic thrombocytopenic purpura (Werlhof's disease) or to rapid loss of platelets from the general circulation as a result of the allergenic action of drugs such as arsphenamine and sedormid and (3) increased capillary permeability owing to nutritional lack

of vitamin B) toxic (infectious diseases) or allergic (food hypersensitivity) causes.

1 SIMPLE PURPURA

It has been possible to demonstrate the presence of an allergic mechanism in some cases of simple purpura. Sachs²⁵³ described petechial eruptions following ingestion of anchovies. Rowe²⁵⁴ reported a similar case. Landsberger²⁵⁵ saw petechial hemorrhages in the skin as well as in the mucosa of the mouth and throat appearing eight days after a nursing first received cow's milk; these symptoms vanished when mother's milk was substituted but reappeared when cow's milk was again given. Watson-Williams²⁵⁶ observed purpura with faucial lesions due to hypersensitivity to neoarsphenamine. FIGURE 382 shows a case of purpura in which allergy to pork was demonstrable.

A nutritive allergic purpura can be differentiated from the nutritive toxic form due to spoiled food by the fact that in the former the manifestations appear after each ingestion of the food in question while toxic purpura occurs only after one particular exposure. Drug allergy can be distinguished from drug toxicity in that small doses suffice to evoke symptoms in the case of the former while only large doses will do so in the latter. In addition to foods and drugs physical agents and autoendogenous allergens can also produce purpura. Thus Yater and Nicklas²⁵⁷ reported an unusual case of allergy to cold exposure to which was always followed by hemorrhagic lesions on the affected parts.

The senior author treated a woman 31 years of age who had suffered for eight years from severe purpura on the thighs and lower parts of the legs appearing after she had been standing or walking for some time and even after sitting for hours. Blood coagulation and bleeding times, platelet count and tourniquet tests were normal. All types of treatment including large doses of ascorbic acid were ineffective. However 5 tablets of histaminase kept the patient symptom free on the day of medication even when she walked for hours at a time. Strangely enough subcutaneous ad

²⁵⁰ BARBER H W. *E t J Dermat* 53 1 33 1941

²⁵¹ RUBIN S S. *Coresponden e J A l e g y* 16 54 1945

²⁵² JAUSION H. *A h derma et syph Hôp St Lou s* 3 541 1931

²⁵³ SACHS O. *Arch f Dermat u Syph* 123 835 1916

²⁵⁴ LANDSBERGER M. *Ztschr f K n d e h* 39 569 1925

ministration of histaminase had no such favorable results.

2. HENOCH'S PURPURA

The term "Henoch's purpura" designates a syndrome in which purpuric attacks are associated with visceral and joint manifestations. It was first described by Henoch in 1868, but did not become widely known until Osler²⁷⁹⁶

and swelling in the joints, gastro-intestinal disturbances (vomiting, abdominal pain, occasionally bleeding from the intestines), and hemorrhagic nephritis. Examination of the blood discloses no change in the clotting and bleeding times, nor in the number of blood platelets. Purpuric hemorrhages cannot be provoked by means of mechanical insults, as in thrombocytopenic purpura. However, an in-

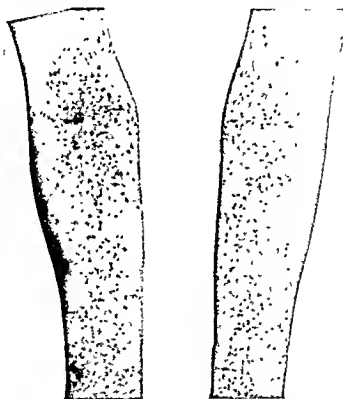


FIG 382 PURPURA DUE TO HYPERSENSITIVENESS TO PORK

published his extensive studies. In 1914 Osler²⁸⁴⁹ suggested that this syndrome might be based on an allergy.

The disease begins with general manifestations, such as malaise, headache, and generalized aching. The skin presents a great many petechiae appearing in showers, the mucous membranes may also be involved, so that occasionally the picture is suggestive of scurvy. The skin manifestations are often polymorphous; that is, in addition to the hemorrhages, there are exanthems of the erythema type, and urticaria, as well as angioneurotic edema—in short, manifestations like those observed in serum sickness. Other commonly encountered symptoms are pains

injection of protein-containing solutions will be followed by cutaneous hemorrhage.

Alexander and Eyermann²⁸⁵¹ demonstrated in a group of cases that elimination of certain food items from the patient's diet prevented the purpura and accompanying intestinal symptoms, while the attacks promptly reappeared after ingestion of the foods in question. The nutritive allergens identified were milk alone; egg, potatoes, and flour; flour and apples; beans; pork, onions; and strawberries, respectively. Some of the corresponding skin tests were positive, some negative. Kahn²⁸⁵⁶ reported the case of woman who had skin, nasal,

and gum hemorrhages as well as digestive disturbances for eight years. Elimination of fish, cereals, and onions from her diet resulted in total disappearance of the symptoms; they reappeared when these foods were again eaten. Another noteworthy observation was made by Barthelme²⁸⁷: a 22 year old girl was suddenly afflicted with epistaxis; three weeks later she began to complain of joint and muscle pains and general malaise. A month later purpura appeared. Although skin testing seemed to disclose polyvalent sensitivities, wheat and egg yolk were the only food items that elicited renewed showers of purpura, along with joint and muscle pain on oral testing, when these foods were eliminated from the diet, the patient remained symptom free. Kern²⁸⁸ treated a patient who had purpura and cutaneous abdominal and renal manifestations all demonstrably due to hypersensitivity to onion. Bisson and David²⁸⁵ studied an 11 year old child with profuse sanguinolent vomiting, a widespread petechial rash becoming purpuric, stupor, bloody stools, and excruciating pain in the epigastric region. An acute abdominal surgical emergency was thought of, but the child improved rather suddenly. He was found sensitive to egg, crab meat, and lima beans. Hampton²⁹⁵ made a very interesting series of X ray pictures of the entire gastrointestinal tract during an attack of purpura caused by milk. Gastric retention and hypermotility together with spasm of the colon were the principal roentgenologic findings. In his 2 cases, as in many others, skin tests with the offending foods were negative, but trial and elimination diets proved very conclusive.

Henoch's purpura is not an extremely rare condition. Eyermann²⁸⁹ alone reported 18 cases. It is estimated by Bisson and David that 95 per cent of cases of Henoch's purpura are subjected to useless surgical intervention such as appendectomy, gastrectomy, or cholecystectomy.

The therapeutic approach to be employed depends largely on the nature of the allergen in the given case. If it is a food or a drug that

may easily be omitted or replaced, its elimination will be sufficient. If an important nutritional protein such as milk or egg is found to be responsible, desensitization by splanchnic procedures such as the administration of propyltans or daily ingestion of cautiously increased amounts of the food will often prove satisfactory. The treatment of the acute episode includes injections of epinephrine to control the abdominal pain, parenteral fluids if necessary, possibly vitamin P to regulate the permeability of the vessels, and symptomatic measures.

In addition to food proteins, there are surely other kinds of allergens responsible for this condition, some of them endogenous, as is shown by Sezary's case^{57*}. For months a man of 30 years had had purpuric exanthems of an urticarial character associated with pains in the joints. It was possible to demonstrate that these attacks were elicited by mild muscular exertion. Intracutaneous injection of a 1 per cent solution of autogenous urinary proteoses evoked a strongly positive skin reaction, while intravenous administration of a 0.01 per cent dilution produced a severe anaphylactic shock. Hyposensitization was achieved by means of subcutaneous injections of peptone and of sodium thiosulfate. Likewise, menstrually recurring purpura of the Schoenlein-Henoch type is thought by Ellman and Weber²⁹⁰ to be of allergic nature.

3. SCHOENLEIN'S PURPURA

Schoenlein's disease (purpura rheumatica or peliosis rheumatica) is the name of a purpuric disorder accompanied by fever, sore throat, and arthritis, as well as by skin manifestations that may be erythematous, urticarial, and even bullous in character. The eruption may last several weeks or months. The constant association of this purpuric disease with chronic infections is responsible for the concept that the condition is an expression of bacterial allergy, with the walls of the blood vessels as the shock structure. For this reason, treatment is directed essentially toward uncovering and eradicating some hidden focus of infection.

²⁸⁷ BARTHELME, F. L. *J. Allergy* 1: 170, 1930.

²⁸⁸ KERN, R. A. *Dis. of the Skin* 1: 100, 1930.

²⁸⁹ EYERMANN, C. H. *South. M. J.* 28: 341, 1935.

²⁹⁰ ELLMAN, W. P. and WEBER, F. P. *Brit. J. Dermat.* 47: 197, 1955.

4. THROMBOCYTOPENIC PURPURA

Thrombocytopenic purpura is characterized by the appearance of countless hemorrhages in the skin, mucous membranes, and internal organs. Examination of the blood reveals, in addition to secondary anemia, a very marked prolongation of the bleeding and coagulation times, as well as a great decrease or almost complete absence of thrombocytes.

Pathogenetically a distinction is made between the essential form, probably of infectious origin (so-called Werlhof's disease) and the allergic form. In the former, the number of the thrombocytes may be extremely small, but they are never completely lacking; furthermore, the platelets present are pathologically altered. In the allergic form, on the other

venous reinjection of the same antigen, and that the extent of the decrease runs parallel to the degree of the shock. And Thiberge⁵⁶³ demonstrated that a marked drop in the platelet count occurs with great regularity during allergic attacks of various types in man.

Schwartz⁵⁶⁴ studied 30 cases of "primary" thrombocytopenic purpura by bone marrow eosinophile counts and concluded that the presence of increased numbers of eosinophils in the bone marrow signified a favorable prognosis for complete spontaneous hematologic and clinical recovery, and splenectomy was unnecessary. There was no correlation between blood and marrow eosinophile counts. Such cases were usually acute in onset and



FIG. 383 THROMBOCYTOPENIC PURPURA DUE TO HYPERSENSITIVENESS TO SEDORMID

hand, the thrombocytes disappear completely in a very short time—this occurred within fifteen minutes in the case reported by Falconer and Epstein⁵⁶¹—but promptly reappear in the circulation following an injection of epinephrine. This is never the case in the idiopathic form. The response to epinephrine is convincing evidence against the assumption of a widespread destruction of the platelets, and suggests that their rapid disappearance from the general circulation into the parenchymatous organs is an expression of a severe allergic reaction. In this connection it is interesting to note the experimental work of Kopeloff and Kopeloff,⁵⁶² who showed that sensitized monkeys present a marked decrease in the number of blood platelets after intra-

course, and were thought to be manifestations of an allergic state, with bacteria, foods, or drugs as the offending allergens. By contrast, cases with few eosinophils in the bone marrow, arbitrarily below 5.0 per cent of the granulocytes of the neutrophilic series, are of poor prognostic outlook and require splenectomy.

Loewy⁵⁶⁵ and Vogl⁵⁶⁶ were the first to demonstrate experimentally the allergic nature of thrombocytopenic purpura following ingestion of sedormid (allyl-isopropyl-acetyl-carbamide); they evoked the same clinical and hematologic disease picture by administering a small dose of the drug orally or parenterally to individuals who had fully recovered from the condition. They also showed that these

⁵⁶¹FALCONER, E. H., and EPSTEIN, N. N. *Arch. Int. Med.* 45, 11-8, 1940.

⁵⁶²KOPELOFF, N., and KOPELOFF, L. M. *J. Immunol.* 40, 471, 1941.

⁵⁶³THIBERGE, N. F. *M. Rec.* 150: 215, 1939.

⁵⁶⁴SCHWARTZ, S. O. *Am. J. M. Sc.* 209: 519, 1945.

⁵⁶⁵LOEWY, F. E. *Lancet* 1, 845, 1934.

⁵⁶⁶VOGL, A. *Wien. klin. Wchnschr.* 45: 906, 1933.

manifestations never appeared after the first dose of the drug but only when it was again taken after a fairly long interval. Since then some 50 cases of purpura caused by sedormid (Fig. 383) have been reported (Huber²⁸⁶⁷ Falconer and Schumacher²⁸⁶⁸ and others). Moreover the literature contains reports of thrombocytopenic purpura due to arsphenamines (Falconer and Epstein²⁸⁶¹) maphar

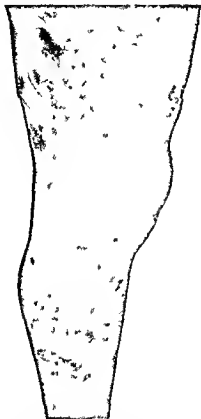


FIG. 384. THROMBOCYTOPENIC PURPURA DUE TO HYPERSENSITIVENESS TO ANCHROVES.

sen (oxophenarsine hydrochloride) (Schwartz and VonderHeide²⁸⁶⁹) gold preparations (Hudson²⁸⁷⁰) quinine (Peshkin and Miller²⁸⁷¹ Beiglboeck²⁸⁷²) ergot (Peshkin and Miller²⁸⁷³)

mirvanol (Jones and Jacobs²⁸⁷⁴) iodine (Denning²⁸⁷⁵) insulin (Strasser²⁸⁷⁶) sulfonamides (Losada and Fernandez²⁸⁷⁶) and salicylates (Ashworth and McKemie²⁸⁷⁷ Rappaport Nixon and Barker²⁸⁷⁸).

However this form of purpura can be elicited not only by drug but also by food allergy (Fig. 384). Thus Squier and Madison²⁸⁷⁹ reported 3 cases in which milk, potato, wheat, cocoa and egg respectively were identified as the allergens and Dutton²⁸⁷⁹ described 1 case due to citrus fruits.

There is only one effective method of treating the allergic form—viz. discovery and elimination of the allergen. In addition symptomatic treatment with injections of epinephrine is useful.

NIDS

The suffix *id* is applied to a peculiar sensitization mechanism of the skin rather than to a clinical disease picture. Or more specifically stated an *id* is the morphologic response of a highly sensitized skin to bacterial or toxic agents emanating from a remote infectious focus or to substances from an allergic tissue carried to the skin by the hematogenous route. This concept is based on the following facts: (1) the *ids* are almost invariably found to be free of micro organisms; (2) the skin in persons with *ids* exhibits a pronounced specifically altered reactivity to extracts of the micro organism in question expressed by a local flare up; (3) the only effective therapeutic approach to *ids* consists in treatment of the primary focus of infection or sensitization.

The *id* phenomena are encountered in many chronic infectious diseases giving rise for example to tuberculous syphilitic leprid trichophytid epidermophytid microsporid monilid and microbid. There are many cases in which under favorable conditions a

²⁸⁶⁶ HUBER H. H. J. A. M. A. 113: 674, 1939.

²⁸⁶⁸ FALCONER E. H. and SCHUMACHER F. C. A. J. Int. Med. 65: 122, 1940.

²⁸⁶⁹ SCHWARTZ M. and VONDERHEIDE E. C. J. A. M. A. 128: 657, 1942.

²⁸⁷⁰ HUDSON E. H. Lancet 2: 71, 1933.

²⁸⁷¹ PESHKIN M. M. and MILLER J. A. J. A. M. A. 102: 1737, 1934.

²⁸⁷² BEIGLBOECK W. Wen. klin. Wchnschr. 51: 487, 1937.

JONES T. D. and JACOBS J. L. J. A. M. A. 99: 18, 1932.

²⁸⁷⁵ DENNING H. Muench. med. Wchnschr. 89: 56, 1935.

²⁸⁷⁶ STRASSER V. Diskussion to Vogt 1934.

²⁸⁷⁷ LOSADA L. M. and FERNANDEZ W. S. Rev. med. de Chile 9: 477, 1942.

²⁸⁷⁸ ASHWORTH C. T. and MCKEMIE J. F. J. A. M. A. 126: 806, 1941.

²⁸⁷⁹ RAPPAPORT A. E., NIXON C. C. and BARKER W. A. J. Lab. & Clin. Med. 30: 916, 1945.

²⁸⁸⁰ DUTTON L. O. J. A. M. A. 111: 1920, 1938.

particular bacterium or fungus was demonstrated in the blood stream. On the other hand, it is hardly ever possible to find these in the "id" itself. J. Jadassohn, to whom we are indebted for this concept, explained this fact on the basis of the rapid destruction, elimination, or attenuation of the living agents by the immune forces of the allergic skin. However, it is distinctly possible that bacterial and



FIG. 385. DERMATID

Following irritating therapy of chronic dermatitis of left foot, disseminated skin eruption of follicular distribution occurred, explainable on basis of id phenomenon.

fungus toxins may produce identical clinical pictures in the allergized skin.

Dermatophytids are rather frequently produced by roentgen irradiation of tinea barbae or tinea capitis, or fungus infections of the feet, by irritating local applications to such dermatoses, by the mechanical influence of friction or pressure, or by injections of trichophyton in too great a concentration. Hellerström²³⁷ reported similar sequelae following irradiation of the buboes in lymphogranuloma inguinale.

More recently, the "id" concept has been broadened to embrace noninfectious and non-

toxic processes as well. Thus, autosensitization, which not too infrequently appears in the course of an allergic dermatitis, is now regarded as an "id" phenomenon. Jaffré²³⁷ has coined the appropriate designation "dermatid" (FIG. 385). An example is offered in the case reported by Shelmire.¹³¹ A patient with poison ivy was patch tested with the specific oleoresin on an excoriated area; he developed not only a local flare-up but also a vesicular eruption on the palms and soles. The concept of "dermatid" and "keratid" is more fully discussed on page 736.

The symptomatology of the "ids" is indeed highly variable. The appearance of an "id" may simulate that of a lichenoid exanthem, such as lichen scrofulosorum, lichen syphiliticus (FIG. 386), and lichen trichophyticus. In other instances it may be vesicular in character, and this type includes, notably, eczematous and pompholyx-like eruptions on the hands of patients with epidermophytosis of the feet; the "id" mechanism has been shown to be present in these cases by Williams,¹³¹⁷ Peck,¹³¹⁶ Weidman,¹³¹⁸ and others. Occasionally, however, the primary focus is located not on the feet but elsewhere—even in the vagina, as in a case of mycotic vaginitis reported by Sutton, Jr.²³¹ Chronic pustular eruptions on the hands and soles (FIGS. 387, 388) that are consistently found to be sterile, have been termed "bacterids" by Andrews and Machacek.²³² Among 24 of their patients presenting this clinical picture, tonsillectomy produced a permanent cure in 9 cases, and marked improvement in 3 cases. In one instance, the skin manifestations definitely regressed every time the pus was expressed from the tonsils; tonsillectomy was followed by complete healing of the skin condition.

Stokes⁶ is of the opinion that certain cases of erythema multiforme and erythema nodosum may well be explained by the "id" concept. Sutton and Sutton²³³ describe "ids" that even resemble pityriasis rosea. Erysipelas-like inflammation of the legs, in the presence of an

¹³¹⁶ WEIDMAN, F. Vegetable Parasitic Dermatoses. In Appleton's System of Medicine, ed. 5, 10: 159, 1917.

¹³¹⁷ SUTTON, R. L., JR. J. A. M. A. 110: 1133, 1933.

¹³¹⁸ ANDREWS, G. C., and MACHACEK, G. F. Arch. Dermat. & Syph. 32: 837, 1935.

²³² SUTTON, R. L., and SUTTON, R. L., JR. Diseases of the Skin, ed. 10. St. Louis: Mosby, 1939.

active epidermophytosis was recognized as an 'id' by Tolmach and Traub^{288a} Sulzberger⁴

fact that monilids—resulting from absorption of a specific substance from a gastro intestinal

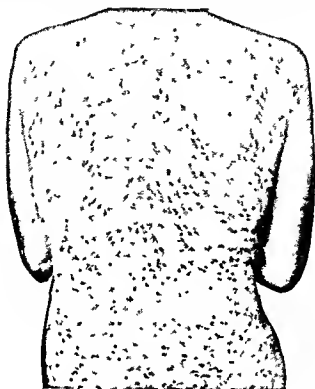


FIG 386 LICHEN SYPHILITICUS

Rare form of cutaneous syphilis probably due to hematogenous distribution of syphilides in specifically allergic skin



FIG 387 BULLOUS ERUPTION ON HANDS (AND FEET) CLASSIFIED AS BACTERID

Cultures repeatedly sterile skin reaction to streptococci strongly positive

and the senior author¹⁸ Lastly Ravaut as well as Hopkins^{288a} called attention to the

tract infected with monilia—may appear clinically as a seborrheic dermatitis

Adequate recognition of the id mechanism on the part of the attending physician can be of decisive therapeutic importance

^{288a} TOLMACH J A and TRAUB E F Arch Dermat & Syph 38 925 1938

^{288b} HOPKINS J G Ibid 29 599 1932

Intensive local treatment of the "id" results only in an exacerbation. Rapid improvement can be achieved, however, by appropriate

O ACNE VULGARIS

Experimental investigations of the past few years have made it clear that the clinical pic-



FIG 388 BACTERID ON SOLES

Recurrent vesiculation for many years cultures always sterile focus of infection not discovered



FIG 389. ACNE VULGARIS WITH EXACERBATION TWO TO FOUR DAYS BEFORE EACH MENSTRUAL PERIOD



FIG 390 DEFINITE IMPROVEMENT FOLLOWING TWO COURSES OF INTRACUTANEOUS INJECTIONS OF AUTOGENOUS SERUM (WITHOUT LOCAL TREATMENT) DURING INTERMENSTRUUM

management of the responsible focus, together with simple local measures, such as application of calamine lotion or 50 per cent alcohol followed by powder.

ture of acne vulgaris can be evoked by a number of different causes, such as disturbances of fat metabolism, focal infection, endocrine imbalances, drugs, intestinal disorders, and emotional factors

In the present discussion only those cases that appear to be of allergic character will be considered. Rowe¹¹⁰ and White²⁸⁸⁶ achieved marked improvement in a considerable number of cases of acneiform eruption by means of elimination diets. Cunningham and Mendenhall²⁸⁸⁷ and Cormia²⁸⁸⁸ also found clinical evidence of food sensitiveness in a number of cases of acne vulgaris. The chief offending foods were found to be chocolate, milk, wheat, oranges, tomatoes and nuts. In cases of this kind skin tests are of no value whatsoever. Stokes and Sternberg²⁸⁸⁹ among others observed decided eruptive flares following ingestion of chocolate, and recovery after rigid exclusion of this item. Sulzberger²⁸⁹⁰ is inclined to suspect that some traces of the chemicals ingested with various foods may irritate the pilosebaceous apparatus, and that therefore the process affecting the sebaceous glands is to be regarded as toxic rather than allergic. Furthermore he calls attention to the fact that even the small quantities of iodine in iodized salt can suffice to cause exacerbation of acne in predisposed individuals. Similarly

spinach, seafood, cabbage and artichokes all have a high iodine content. Likewise Sulzberger does not consider the aggravation of the condition that sometimes occurs after ingestion of white bread to be evidence of specific food hypersensitiveness, but believes it to be caused by improvers in the bread, these contain potassium bromate which is reduced to bromide in the process of baking. Thus the good effect of elimination diets is not necessarily convincing proof of a nutritional allergy.

Moreover we⁸⁷ are of the opinion that at least some cases of menstrual acne are of endogenous allergic nature. We refer to those rather commonly observed patients in whom there is a visible flare up of acne lesions a few days before each menstrual period (Figs 389, 390). In many such cases the menses are inclined to be scant or irregular and titration of the urine gives abnormally low values for estrogenic hormones. Treatment may be carried out with blood withdrawn before menstruation at the height of the acne symptoms. During each of two intermenstrual intervals, the patient is given a course of nine to eleven intracutaneous injections, each of 0.2 cc of autogenous serum, administered every second day. The favorable effect of this treatment speaks for the mechanism of endogenous allergy in such cases of acne rather than that of menstrual toxicosis (see p. 836).

¹¹⁰ WHITE C. J. A. M. A. 103: 127, 1934.

²⁸⁸⁶ CUNNINGHAM T. D. and MENDENHALL J. C. J. Allergy 7: 378, 1936.

²⁸⁸⁷ CORMIA F. E. b. d. 12: 34, 1940.

²⁸⁸⁸ STORER J. H. and STERNBERG T. H. Arch. Dermat. & Syph. 40: 345, 1939.

²⁸⁸⁹ SULZBERGER M. B., ROSTENBERG A. J. and SHER J. J. New York State J. Med. 34: 899, 1934.

CHAPTER XXVI

ALLERGIC DISEASES OF THE NERVOUS SYSTEM

THE results of experimental investigations in the past few years permit the assumption that the central nervous system as well as the peripheral nerves can be allergized, and consequently are subject to allergic diseases. The subsequent cerebral or neurologic manifestations may be based on any of a variety of mechanisms (Urbach and Gottlieb²³¹). In the majority of cases—at least in human beings—there is an underlying vascular allergy. The reason why this is confined to the cerebrum or the peripheral nervous system may be found in certain predisposing factors, such as hereditary predisposition (to headaches, migraine, etc.), local infection, local trauma, and possibly psychosomatic influences. Any one of these factors is capable of creating, so to speak, a *locus minoris resistentiae*. Vascular allergy can bring on cerebral angiospasm or cerebral angioneurotic edema, either of which can in turn produce a great variety of clinical symptoms. These will be discussed in some detail below. When an allergic reaction occurs within the cranial cavity, the localized edema may increase intracranial pressure and simulate brain tumor, or the local anemia may cause various transient neurologic symptoms (Clarke²³²). The recognized symptoms of increased intracranial pressure are headache, vomiting, dizziness, symptoms referable to pressure on the optic nerve, convulsions, hyperesthesia, anesthesia, paralysis, and psychosis.

Only in a small percentage of cases are parenchymatous changes found. These point to allergization of the nervous tissue itself, in either the central or the peripheral nervous system.

Finally, the significance of certain disturbances of the autonomic nervous system in the elicitation and maintenance of allergic processes is becoming more and more apparent. It is now generally assumed that all allergic phenomena are under parasympathetic control.

A THE EXPERIMENTAL BASIS OF ALLERGIC PHENOMENA OF THE CENTRAL NERVOUS SYSTEM

Changes in the brain due to local anaphylaxis of the type of the Arthus phenomenon must be differentiated from those caused by generalized anaphylactic shock.

I PATHOLOGIC CHANGES IN THE BRAIN ASSOCIATED WITH LOCAL ANAPHYLAXIS

Local anaphylactic reactions of the central nervous system have been demonstrated by two methods, namely, intracarotid reinjection and direct application of the antigen to various parts of the brain. When, in experiments with sensitized dogs, the allergen, in amounts ineffective on intravenous administration, was reinjected into the carotid artery in the cephalad direction, a distinct fall in blood pressure was observed (Spiegel and Kubo²³³). The assumption that this was due to a local reaction of the vasomotor center was confirmed by the fact that a later intravenous injection of a larger dose, acting on the body as a whole, served to elicit a second drop in blood pressure.

The method of direct application was successfully used by Hashimoto.²³⁴ He injected small amounts of antigen into the corpus striatum in sensitized rabbits and observed a fall of body temperature similar to that produced by the intravenous injection of large amounts of antigen. The duration and the magnitude of the drop were strictly parallel to the degree of sensitization. This reaction occurs only on administration of the specific antigen, and cannot be called forth in specifically desensitized animals. He concluded, therefore, that the thermoregulatory center—or more precisely, the ganglion cells forming the center—had been highly sensitized by the preparatory administration of the foreign pro-

²³¹ SPIEGEL, E. A., and KUBO, K. *Ztschr. f. d. ges. exper. Med.* 33: 473, 1925.

²³² HASHIMOTO, M. *Arch. f. exper. Path. u. Pharmacol.* 73: 370, 1912.

²³³ L. BRACH, E., and GOTTLEB, P. M. *Concilia neurol.* 3: 135, 1942.

²³⁴ CLARKE, T. W. *Ann. Allergy* 2: 129, 1944.

tein Davidoff and Kopeloff²⁸⁹ applied various allergens directly to the brains of dogs through a craniotomy. No symptoms followed this first application. Several days later the animals were given intravenous injections of the sensitizing substance. Within a few minutes convulsions and definite signs of weakness were observed on the opposite side of the body in muscle groups corresponding to the motor areas of the brain to which the antigen had been applied. This was interpreted by the authors as evidence of localized cerebral allergization.

Tokushige²⁹⁰ sensitized rabbits by means of intracerebral injections of foreign serum. When the reinjection was given intravenously general anaphylaxis resulted along with a marked drop in cerebrospinal fluid pressure and blood pressure. When on the other hand the reinjection was given cerebrally only a local cerebral Arthus phenomenon resulted with a rise in cerebrospinal fluid pressure and no change in blood pressure. This may be explained by the fact that the local inflammatory swelling produced by the local brain anaphylaxis raised the intracranial pressure.

Alexander and Campbell²⁹¹ studied local anaphylactic lesions of the brain in guinea pigs. While the sensitizing doses were administered intraperitoneally or subcutaneously the shocking injection was given intracerebrally. The result was an extensive inflammatory lesion in the brain characterized by hemorrhage, edema, leucocytic infiltration and serum exudation.

In their work on monkeys Jervis Ferraro, Kopeloff and Kopeloff²⁹² recognized two principal types of lesions. The first is a local reaction at the site of the intracerebral injection of the antigen and this they regard as a typical Arthus phenomenon. In the center of this lesion all the elements of the tissue appear to be destroyed at the periphery, however, chiefly the myelin sheaths are involved while the axis cylinders and glia are in a better state of preservation. The blood

vessels within the necrotic lesion show thickening of the walls, thrombosis and obliteration of the lumen by connective tissue. The authors point out that when the differences in the fundamental structures of the nervous tissue are taken into consideration no significant deviation from the Arthus phenomenon observed in other viscera can be recognized as far as the quality of the lesion is concerned.

The second outstanding type of lesion is found in scattered parts of the brain—in areas far from the local alteration produced by the injection of the antigen. These lesions consist of circumscribed foci disseminated throughout the white matter of the brain, cerebellum and medulla and composed of glial cells, relatively few hematogenous elements and peculiar giant cells. As to their origin the authors venture the interesting hypothesis that the pathologic changes in the brain are due to brain specific antibodies, the reacting antigen being a lipid contained in the ether alcohol extract and activated by protein present in the emulsion of heterologous brain. In a more recent reevaluation of these neuro-pathologic changes Ferraro²⁹³ concluded that both types of inflammatory vascular changes in the central nervous system, whether at the site of the antigen injection or at a distance, are the expression of a hyperergic type of inflammation.

Lewis²⁹⁴ showed that alcoholic extracts of brain tissue are iso antigenic, this being the first demonstration of the iso antigenicity of a tissue lipid. The important question of the formation of brain specific antibodies will be discussed below. Adolf²⁹⁵ had pointed out previously that the myelitides observed as a complication of the Pasteur treatment of rabies may be due to the formation of antibodies produced by the repeated injection of lipid substances into the body.

Solowjew and Ariel were able to produce allergic inflammation of the brain by introducing both the sensitizing and eliciting injections of horse serum into the subarachnoid space by means of suboccipital puncture without stunning the animals.

The term "carotid syndrome" was used by

²⁸⁹ DAVIDOFF S. M. and KOPELOFF N. *J. Lab. & Clin. Med.* 20: 1238, 1935. *J. Immunol.* 30: 477, 1937.

²⁹⁰ TOKUSHIGE J. *Okayama Igakka Zasshi* 49: 2187, 1937.

²⁹¹ ALEXANDER L. and CAMPBELL A. C. P. *Am. J. Path.* 43: 229, 1937.

²⁹² JERVIS G. A., FERRARO A., KOPELOFF L. and KOPELOFF N. *Arch. Neurol. & Psych.* 45: 733, 1943.

²⁹³ FERRARO A. *J. Neuropath. & Exper. Neurol.* 4: 1, 1945.

²⁹⁴ LEWIS J. H. *J. Immunol.* 41: 397, 1941.

²⁹⁵ ADOLF M. *Jahrb. f. Psychiat. u. Neurol.* 43: 51, 1924.

Forssman²⁹⁰² to designate the neurologic disturbances induced in the guinea pig by the intracarotid injection of a small amount of serum containing Forssman antibodies. The syndrome consists of dysequilibrium, rotary movements of the eyeballs, and nystagmus. Jervis²⁹⁰³ found the pathologic changes underlying this entity to consist of diffuse degenerative changes of the nerve cells and circumscribed foci of demyelination with a roiroglial reaction—the picture of “multiple degenerative softenings.” These parenchymatous lesions are considered to be anaphylactic in nature, resulting from the reaction between the injected Forssman antibodies which have passed through an impaired hematoencephalic barrier and Forssman antigens normally present in the tissues of the guinea pig.

2. PATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM IN GENERALIZED ANAPHYLACTIC SHOCK

According to Weinberg and to Stief and Tokay, two types of diffuse lesions—vascular and parenchymatous—are manifested by animals dying from experimentally produced, protracted anaphylactic shock, which, as is known, is regularly accompanied by severe cerebral manifestations. The vascular lesions are characterized by perivascular round cell infiltration, hemorrhages, and occasionally thrombosis; the parenchymatous, by diffuse degenerative changes in the nerve cells. When the anaphylactic shock is of long duration, areas of encephalomalacia are apparent in the sections (Dechaume and Croizat). Garcia and Bertrand described degenerative changes with sclerotic areas of microglia after repeated shocks elicited by injections of foreign serum in animals. In both localized and generalized experimental anaphylaxis, constriction of the pial vessels might be expected. This cannot be demonstrated, however, owing to the concomitant vasodilatation caused by the associated asphyxia (Finley). But Buermann and Alexander²⁹⁰⁴ succeeded in producing homolateral constriction of the cerebral vascular bed, apart from the anaphylactic shock, by means of intracarotid injections.

Miyahara²⁹⁰⁵ demonstrated that injection of the protein antigen into the blood stream of allergized animals brings on hemorrhagic infarcts in the brain, while introduction into the cisterna causes leptomeningitis and “inflammation of the blood vessels.”

As has been mentioned above, a predisposing factor—creating a cerebral *locus minoris resistentiae*, so to speak—is essential to the development of allergic manifestations in the brains of animal species that do not, like the guinea pig, regularly respond to shock with cerebral vascular spasms. Thus, Davidoff and Kopeloff²⁹⁰⁶ showed that it is possible allergically to produce hemiplegia in allergized dogs by supplementing the preparatory intravenous horse serum injection with an intracerebral injection of serum plus agar, thus creating a local inflammatory focus.

Furthermore, recent investigations indicate that the central neurones may be primarily involved in reactions that at first glance appear to be due to allergization of the peripheral nerves. Thus, as Marbais²⁹⁰⁷ pointed out, the exposed sciatic nerve—for example, in a rabbit or guinea pig sensitized to human serum—manifests a decreased faradic excitability for some two to three hours after the nerve has been wet with a few drops of the serum, while no such change is to be observed when serum of any other origin is employed. The nerve in nonallergized animals gives no evidence of an altered degree of excitability following application of human serum. Marbais maintains that this electric hypo-excitability is attributable to a change in the function not of the nerve itself, but rather of the central neurones. This is shown by the fact that when the nerve is severed, it does not react in this way to contact with the antigen, nor does it do so in a state of narcosis, in which cerebral function is suspended. On the other hand, when Marbais injected the antigenic serum into one hemisphere of the brain, he found that the faradic excitability of the opposite part of the body was lowered, and called this *hemianaphylaxis*.

These experiments justify consideration of this nervous hypoexcitability as an allergic

²⁹⁰² FORSSMAN, J. Acta path et microbiol Scandinar. 3: 749, 1926.

²⁹⁰³ JERVIS, G. A. Arch Path 35: 560, 1943.

²⁹⁰⁴ BUERMANN, A., and ALEXANDER, L. Confina. neurol. 2: 715, 1939.

²⁹⁰⁵ MIYAHARA, K. Psychiat et neurol japon 42: 679, 1938.

²⁹⁰⁶ DAVIDOFF, S. M., and KOPELOFF, N. Proc Soc Exper Biol & Med 29: 71, 1931.

²⁹⁰⁷ MARBAIS, S. Schweiz med Wchnschr 63: 669, 1933.

phenomenon. From this standpoint the drop in arterial blood pressure as well as the prelethal loss of vascular tonus seen in anaphylactic shock may be due at least in part to hypo excitability of the vasomotor center on an allergic basis.

3 IMPORTANCE OF PHYSIOLOGIC NERVOUS CONTROL ON THE COURSE OF ALLERGIC TISSUE REACTIONS

Physiologic nervous control is of the greatest importance in the course of allergic hyperergic tissue reactions. Lasowsky,¹⁰⁰ Wyropajew and Jurmann¹⁰¹ showed that a brief irritation of the nerve leads to an increase in the hyperergic inflammation in the tissues. In denervated tissue however according to Wyropajew the picture is quite different: about six to ten days after the nerve has been severed the hyperergic reaction is definitely reduced between the tenth and thirtieth day the reaction if any is very weak and thereafter when trophic disturbances are present it is impossible to evoke any such reaction at all.

Similarly Buchwald¹⁰² showed in animal experiments that elicitation of allergic reactions in the affected extremities is inhibited after the sensory nerve fibers are severed. Similar observations were made in the case of a patient suffering from tabes who had lost almost all sensation in the lower extremities.

On the other hand Kaiserling and Mathies¹⁰³ found that blocking of the nerve action facilitates the development of the allergic tissue reaction in the region supplied and also aggravates its course. Bereston¹⁰⁴ also found that in experimentally produced allergic contact dermatitis in patients with neurologic disorders (transverse cord lesions, hemiplegia) the reactions were stronger on the normal skin than on that of the affected side but no such differences existed with respect to intracutaneous tests with tuberculin or trichophyton.

All of this indicates the extraordinarily important role of the peripheral nervous system in the development of hyperergic inflammations.

4 THE AUTONOMIC NERVOUS SYSTEM AND ALLERGY

In animal experiments it is possible to accelerate the course of an inflammation in the cutis by sectioning the sympathetic innervation. The same result can be achieved by stimulating the vagus nerve. On the other hand inflammation will fail to develop after the vagus has been severed. Of a number of experiments available the one reported by Kaiserling¹⁰⁵ might be cited since it seems to be especially characteristic.

Under normal conditions introduction of serum into the lumen of the appendix of serum sensitized animals does not lead to any inflammatory reaction of the appendix. On the other hand when the antigen is thus administered after extirpation of the vasoconstrictors in the splanchnic nerves or after stimulation of the vagus appendicitis ensues. Under otherwise identical experimental conditions stimulation of the sympathetics or section of the vagus inhibits the inflammatory hyperergic reaction.

These studies provide the experimental basis for the view that changes in the tone of the parasympathetics are significant factors in the production of allergic reactions. The tone may be lowered as in allergic circulatory shock or raised as in bronchial asthma and allergic gastro intestinal diseases. Clinical observations lend additional support to this view. It is well known that an allergic individual almost invariably has a labile vegetative nervous system. By temporary inhibition of the vasoconstrictors and stimulation of the vasodilators it is possible to produce changes in motility secretion and absorption—changes demonstrable in many allergic syndromes in man.

5 IS THE CENTRAL NERVOUS SYSTEM CAPABLE OF CREATING ANTIBODIES?

Is the central nervous system dependent upon the antibodies of the blood or is it capable of creating antibodies itself? For many years the pathogenesis of tertiary neurosyphilis was assumed to be due to the immunologic weakness of the nervous system. This opinion was based on the observation

¹⁰⁰ LASOWSKY J. M., WYROPJEW D. A. and JURMANN M. A. *Vierteljahrsschrift für path. Anat.* 27: 334 1930.

¹⁰¹ BUCHWALD H. *Med. Klin.* 36: 1307 1940.

¹⁰² KAISERLING H. and MATHIES W. *Vierteljahrsschrift für path. Anat.* 29: 48 1935.

¹⁰³ BERESTON E. S. *J. Invest. Dermatol.* 4: 75 1944.

¹⁰⁴ KAISERLING H. *Deutsche med. Wochenschr.* 63: 459 1937.

that the nervous system apparently possesses an impermeable barrier between the blood and the spinal fluid, and so does not share in the antibodies circulating in the blood stream. But more recent observations—in syphilis of the central nervous system—seem to refute the earlier assumption. For more and more cases have been observed in which, after vigorous treatment, the spinal fluid was found to contain Wassermann reagins in considerable titer. According to the modern view (p. 472), these must be regarded as genuine although unusually constituted antibodies. We are indebted to Plaut²⁹² for the first definite proof of the fact that the central nervous system is capable of forming antibodies. By means of a special experimental technic applied in rabbits, he demonstrated that the nervous system can, after preparatory local treatment, produce all the usual antibodies (hemolysins, agglutinins, etc.) as well as Wassermann reagins. Illert reported similar findings. On the basis of parallel titrations for syphilitic antibodies and isoagglutinins made on the serums and spinal fluids of patients with neurosyphilis, Wiener and Derby²⁹³ likewise concluded that the syphilitic reagin in the spinal fluid of such patients is at least in large part formed locally. These authors have not as yet been able to discover in precisely what part of the nervous system these antibodies are produced.

In this connection the investigations of Bailey and Gardner²⁹⁴ are interesting. These would indicate that the brain and other parts of the nervous system are capable of acting as antigens. Immunization of rabbits with heat-killed vaccine of *Pasteurella bovisseptica* (grown in an infusion broth prepared from rat brain) resulted in production of antisera containing antibodies to the broth as well as to the bacteria. Guinea pigs passively sensitized with these antisera and injected intravenously twenty-four hours later with autoclaved extracts of various organs of rats responded with severe or fatal anaphylaxis only to the extract of brain tissue. Similar

results were obtained when white matter of normal ox brains or the brains of rabbits experimentally infected with rabies were substituted for rat brain. The lipid fractions of brain tissue were not anaphylactogenic. Kopeloff and Kopeloff²²³ also demonstrated anti-brain antibodies in the serum of immunized rhesus monkeys. Complement-fixing antibodies were found in the serum of schizophrenic patients after insulin shock therapy by Read, Heilbrunn, and Liebert.²²⁷

B ALLERGIC DISEASES OF THE CENTRAL NERVOUS SYSTEM

The foregoing review shows that there is justification for speaking of allergic diseases of the central nervous system. These conditions manifest themselves in various clinical syndromes: as persistent headaches, as periodic headaches with vomiting (migraine), as convulsive states (epilepsy), as cerebral hemiplegias and monoplegias, encephalomyelitis disseminata, pseudotumor, Landry's paralysis, Ménière's syndrome, neuritis and polyneuritis, and, finally, as certain psychic disturbances. But we must emphasize that, in all cases presenting any of the clinical pictures just mentioned, it is of course imperative first to search for an organic cause. Moreover, one is justified in considering a manifestation as allergic only after appropriate elimination and re-exposure tests have been positive.

1. ALLERGIC HEADACHES

Eyermann²⁹⁵ suggested that the term "allergic headache" be applied to headaches that can be proved to be due to hypersensitivity, but that cannot properly be called migraine because cerebral cortical symptoms are lacking.

Although diffuse headaches can, of course, be due to any of a great variety of causes, the possibility of an allergic origin should always be considered in doubtful and puzzling cases.

According to Schueller and Wilder,²⁹⁷ allergic headaches are usually diffuse, although as a rule they start locally, most frequently in the forehead, over the glabella, about the eyes, or in the back of the head. They usually

²⁹² PLAUT, F. *Zentralbl. f. d. ges. Neurol. u. Psychiat.* 49: 735, 1928.

²⁹³ WIENER, A. S., and DERBY, I. M. *Proc. Soc. Exper. Biol. & Med.* 38: 457, 1938.

²⁹⁴ BAILEY, G. H., and GARDNER, R. E. *J. Exper. Med.* 72: 499, 1940; *Am. J. Hyg.* 34: 205, 1942.

²⁹⁵ EYERMANN, C. H. *J. Allergy* 2: 106, 1931.

²⁹⁷ SCHUELLER, A., and WILDER, J. *Der Kopfschmerz*. Berlin: Springer, 1934.

begin within three hours after exposure to the allergen, sometimes the delay may be as long as eight to twelve hours. A given patient generally will respond regularly in the same length of time. The duration is variable. Without treatment the condition may persist for from ten to twenty-four hours, occasionally for several days; its severity is dependent upon the quality and quantity of the allergen involved. The headaches often begin with a feeling of "stiffness" in the nose and with a watery nasal discharge; they are less frequently accompanied by dizziness, abdominal manifestations (nausea, vomiting, stomach ache, diarrhea), occasionally by edema of the face, and rarely by edema of the extremities. In addition, according to Estru and Dumm,²⁹¹³ marked asthenia and mental disturbances, such as loss of memory and somnolence, are often present. In women, the condition tends to be worse during the menstrual period.

Mention of allergic manifestations is often found in both the family and personal histories of these patients.

The allergens are usually foods, occasionally inhalants. They can be identified by the methods of elimination and re-exposure, the propeptan diet, and, when necessary, skin tests.

Allergic headaches are possibly produced by edema in the brain not unlike angioneurotic edema of the skin.

As an example, we may cite briefly the case of a colleague who, at about the age of 20, began having occasional headaches in the morning. At about noon these would become very severe, almost unbearable, toward evening, they would diminish. It eventually occurred to him that he always suffered from these morning headaches when he had eaten chocolate the previous evening. He carefully eliminated chocolate from his diet, and this resulted in complete relief from the headaches.

Crowe²⁹¹⁴ reported the case of a 9-year-old boy with severe unilateral frontal headaches sometimes preceded by a swelling of the lips and eyelids. Skin tests revealed positive reactions to various foods of vegetable origin. Elimination of the offending ingestants led to disappearance of the headaches and the facial

edema. Addition of wheat to the diet again produced both symptoms.

Treatment consists, of course, primarily in combating the underlying hypersensitivity. Additional measures are symptomatic administration of epinephrine or ephedrine, intravenous injections of calcium, and, under some circumstances (see below) histamine desensitization.

In this connection the observation of Winkelman and Moore²⁹²⁰ is noteworthy. These authors report a case of severe allergic headaches due to ephedrine. The symptoms disappeared when the patient discontinued an ephedrine nasal spray that had been ordered for a nasal allergy, and they recurred with renewed use of ephedrine.

2 MIGRAINE

The term migraine designates paroxysmal headaches that are usually characterized, in the beginning at least, by a unilateral involvement and by a severity that may totally incapacitate the patient. These headaches are usually preceded by visual symptoms and are often associated with gastro-intestinal phenomena, such as nausea and vomiting. This explains the layman's designation of the condition as a "sick headache" or a "bilious headache."

It is now generally accepted that migraine is merely a symptom complex and not an etiologically distinct entity. Numerous investigations undertaken during the past few years permit the assumption that one of the more important causes of migraine is hypersensitivity to certain foods and occasionally to certain inhalant allergens.

It is imperative, however, to make sure in each individual case that the headaches are not due to an eye, ear, or cerebral disease, that the condition is not attributable to a sinus, tonsillar, dental, or systemic infection, gastro-intestinal or other intoxication, a liver or kidney disorder, or endocrine or metabolic disturbance, and that there are no underlying angiospasm. In other words, the possibility of an allergic origin is to be investigated only after the possibility of organic disease, and of

²⁹¹³ Estru, M. and Dumm, J. F. *Rev. med. cir. do Brazil* 23: 1944.

²⁹¹⁴ Crowe, W. R. *J. Allergy* 13: 173, 1942.

²⁹²⁰ Winkelman, A. W., and Moore, M. T. *J. Nerv. & Ment. Dis.* 93: 736, 1941.

all conditions leading to vascular spasm, has been systematically ruled out.

a) PATHOGENESIS OF MIGRAINE

Countless theories have been advanced to explain migraine. The best known of these attribute the condition to disturbances of endocrine function, particularly of the ovaries; to acute swelling of the hypophysis; to auto-intoxication following chronic constipation or duodenal stasis; and to reflex action from eye-strain due to refractive errors. It must be granted that such disturbances are of some significance in the production of migraine, but they certainly do not suffice to explain the

the former and acetylcholine in the latter type (Goldkuhl²⁹²).

Atkinson²⁹³ carries this concept one step further. He holds that the patients with "red" migraine are histamine-sensitive, showing a positive wheal reaction with pseudopodia to an intradermal skin test with 0.1 cc. of a solution of histamine salt in a concentration of 1:20,000 (calculated in terms of histamine base), while those with a normal or histamine-insensitive reaction (the "white" or "non-allergic" group) owe their associated symptoms, especially scotomata, to a primary vasoconstriction followed secondarily by a vasodilatation producing the headache (Fig. 391). In this respect, migraine is basically

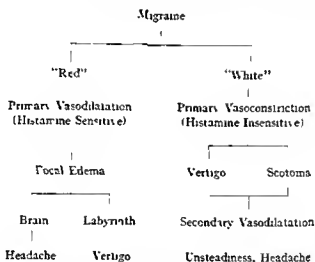


FIG. 391 DUAL MECHANISM IN MIGRAINE (ATKINSON²⁹³)

entire pathogenesis of the disease. Widespread acceptance has been accorded the vasomotor theory which accounts for the various phases of migraine on the basis of disturbances of the cerebral vasculature mediated by the autonomic nervous system. This theory assumes the presence either of vasoconstriction, due to irritation of sympathetic nerves, to explain the "white (pale) migraine"; or of vasodilatation, due to paralysis of the sympathetics or to stimulation of dilators, to account for the "red migraine." Some authors are of the opinion that the vasodilatation may result from prolonged vasoconstriction, while others differentiate sharply between an angiospastic and an angioparalytic type, partly on the ground that the only effective therapeutic measures are administration of gynergen in

comparable to Ménière's syndrome, which can be considered a type of aural migraine. He encountered both conditions in some patients, and others in whom migraine symptoms merged into Ménière attacks. They differ in the location of the impact—the cerebral hemisphere being involved in migraine, the labyrinth in Ménière's—although what determines location or laterality is not apparent. They also differ in the frequency of occurrence of the two groups, the primary vasodilator being relatively small in Ménière's syndrome, while in migraine the proportion, if not reversed, is at least more nearly equal. In Atkinson's opinion, rational therapy of each type should

²⁹² GOLDKUHLE, E. *Acta psychiat. et neurol.* 10, 33, 1935.

²⁹³ ATKINSON, M. *Ann. Int. Med.* 18, 797, 1943.

be directed to the underlying vascular dysfunction and requires different measures. According to Farmer⁴²⁵ the present authors and others however actual histamine sensitivity does not occur without denying that release of histamine from the tissues may play a part in vascular headaches. In cases with recurring headaches when no organic cause can be found and dietary measures do not cause improvement Lieder³³ advocates a provocative histamine test by giving 0.3 mg. of histamine base subcutaneously as originally suggested by Horton³²⁴.

Pelner and Aibel³²⁵ have attempted to distinguish a group of vascular headaches in patients skin sensitive to acetylcholine as well as to histamine and have based a new prostigmine therapy on this theory.

The fact that vasomotor changes in the blood vessels of the brain are responsible for migraine attacks was proved experimentally so to speak by Goltman³⁹⁶. His patient a woman who had suffered from migraine for years had symptoms suggestive of a brain tumor and an exploratory craniotomy was therefore performed. Operation revealed a tense nonpulsating dura. When the dura was opened a considerable amount of fluid was expelled under increased pressure. On this basis the diagnosis was revised to that of cerebral edema and idiopathic migraine. A depression about 1 inch in diameter remained after the operative wound had healed enabling Goltman to make the following important observations. After ingestion of certain foods especially wheat attacks of migraine regularly occurred in about twenty-four hours. They were initiated by vasomotor spasm manifested by blanching of the face which increased to the point of a well defined pallor before the onset of the headache during this phase the usual depression in the region of the opening in the patient's skull was still present. With the onset of the headache however a visible and palpable swelling tense and definitely fluctuating became evident at this site. Goltman explains this as a second

ary vascular dilatation with resulting edema of the brain. The latter is responsible for a temporary disproportion between the volume of the cranial contents and that of the cranial cavity thus causing the severe headache.

If Goltman's observation may serve as a basis for generalization some cases of migraine are to be regarded as a local cerebral angioneurotic edema just as various other allergic manifestations in other organs are known to be due to angioneurotic edema. Quincke⁷⁹⁴ held the somewhat similar view that migraine is caused by a circumscribed edema of the meninges. He based this assumption on the observation that 7 of his patients who suffered from angioneurotic edema were subject to sudden attacks of migraine like headache. This idea finds further support in the investigations of English roentgenologists. Diodrast was injected into the carotid arteries during the prodromal stage of migraine. In this phase the arteries of the brain appeared sharply and clearly outlined but when the diodrast was injected after the headache had really started the outline of the cerebral arteries was hazy. This change was interpreted as indicating that the cerebral arteries were in a state of spasm thus forcing some plasma into the perivascular tissues. This they believe causes the headaches which wane and finally disappear as the extravasated serum is resorbed.

This concept was indirectly confirmed by the observation of Redisch and Pelzer²⁹⁷ that there is a regular tendency of the capillaries of the skin at the cuticle base and of the mucosa of the lower lip to become indistinct or blurred in outline during migraine attacks. Following an injection of ergotamine tartrate there was a definite increase in capillary visibility. These authors believe that the distinctness of the capillary outlines is directly related to the transudation or exchange of fluid through the capillary wall. Presumably the cerebral vessels undergo similar changes. Since forced water intake resulted in migraine attacks in the majority of instances in the period of water retention following the period of excess excretion along with an associated blurring of the capillaries they concluded that there is a relationship between the fluid balance

³²⁴ LIEDER, L. E. *Letters Internat. Coll. Club of Allergy* 1943 p. 1.

³²⁵ HORTON, B. T. *JAMA* 116: 377, 1941.

³⁹⁶ PELNER, L. and AIBEL, M. E. *J. Lab. & Clin. Med.* 27: 1516, 1942.

⁷⁹⁴ GOLTMAN, A. M. *J. Allergy* 7: 351, 1936.

²⁹⁷ REDISCH, W. and PELZER, R. H. *Ann. Intern. Med.* 26: 298, 1933.

of the body, the state of the peripheral capillaries, and the migraine attack. Mueller²⁹²³ had previously pointed out that persons with changes in capillary form and diameter tend to have an increased susceptibility to vaso-motor disturbances, allergic predisposition, and migraine.

In opposition to the concept that vasoconstriction followed by vasodilatation is the cause of migraine attacks, Graham and Wolff²⁹²⁹ have developed the theory of hypotonia and distention of certain cranial arteries. These authors base their stand on the fact that all the substances capable of reducing the amplitude of pulsation of the cranial vessels also serve to abate the pain in migraine. Schumacher and Wolff²⁹³⁰ found that the pain in migraine headaches is independent of changes in intracranial pressure. They suggest that the preheadache disturbances result from occlusive vasoconstriction of the cerebral arteries, while the headache itself is caused by dilatation and distention of the branches of the external carotid arteries, the relief afforded by pressure around the head would confirm this concept. On the basis of careful studies of the effect of ergotamine tartrate in migraine, Pool, von Storch, and Lennov²⁹³¹ agreed that the pain is not explained by an abnormality of intracranial pressure or spasm of cerebral vessels. Von Storch²⁹³² tentatively suggested that the mechanism consists of overstimulation of the dural, and possibly extracranial, periarterial plexuses through the medium of hypotonic dilatation of the vessels in question. On the other hand, Scott²⁹³³ places the dilatation in the meningeal arteries, and Best and Taylor²⁹³⁴ in the pial vessels, preceding spasm accounting for the prodromal symptoms. Torda and Wolff²⁹³⁵ have recently pointed out that after several hours of migraine the branches of the external carotid arteries

become more prominent, pipelike, and less readily compressible, and that the pulsating or throbbing nature of the headache may turn into a steady ache. They postulated that after sustained dilatation, thickening or edema of the muscular and adventitial structures of the vessels occurs. Microscopic examination of sections of the temporal artery of patients during attacks of migraine actually revealed thickening of the arterial wall.

In summary, a mass of evidence indicates that migraine is of vascular origin, although there is no agreement on the location, nature, and sequence of the vascular changes.

b) ALLERGIC BASIS OF MIGRAINE

For over a century the French have been calling attention to the high incidence of migraine in patients with asthma, dermatitis, and urticaria. But it was not until some thirty years ago that the allergic nature of many cases of migraine was first demonstrated by Laroche, Richet, Jr., and Saint-Girons,¹⁹³⁷ then by Pagniez and his collaborators²⁹³⁶ in France, and by Brown²⁹³⁷ in America. However, credit must be given to Vaughan,²⁹³⁸ Balyeat,²⁹⁴⁴ Eyermann,²⁹⁴⁸ and Rowe²⁹³⁹ for employing conclusive elimination and exposure experiments, on large series of cases, to prove the importance of allergy in the etiology of migraine.

The allergen is likely to be a food, usually a food of vegetable origin. Lieder²⁹⁴⁰ found hypersensitiveness to food in 28 of 52 patients, 23 of whom had other major allergic diseases. Wheat has most commonly been identified as the causative agent (Tuft,²⁹⁴¹ Hill,²⁹⁴² Goltman,²⁹²⁶ Vaughan,²⁹²⁸ Conwell and Kurth,²⁹⁴³ and others). Chocolate is in second place (Pagniez,²⁹³⁶ Hill,²⁹⁴² Vaughan,²⁹⁴¹ Balyeat,²⁹⁴⁴ Urbach). Alvarez²⁹⁴⁵ lists the offenders in order of frequency as chocolate, onions, milk, peanuts, cabbage, eggs, pork, apples, coffee,

²⁹²³ MUELLER, O. *Schweiz med. Wchnschr.* 70: 17, 1940.

²⁹²⁹ GRAHAM, J. R., and WOLFF, H. G. *Arch. Neurol. & Psychiat.* 39: 731, 1938.

²⁹³⁰ SCHUMACHER, G. A., and WOLFF, H. G. *ibid.* 45: 199, 1941.

²⁹³¹ POOL, J. L., VON STORCH, T. J. C., and LENNOV, W. G. *Ann. Int. Med.* 57: 32, 1936.

²⁹³² VON STORCH, T. J. C. *New England J. Med.* 217: 217, 1937.

²⁹³³ SCOTT, J. W. *Canad. J. A. J.* 45: 343, 1941.

²⁹³⁴ BEST, C. H., and TAYLOR, N. B. *Physiologic Basis of Medical Practice*. 2d ed. Baltimore: Williams & Wilkins, 1940.

²⁹³⁵ TORDA, C., and WOLFF, H. G. *Arch. Neurol. & Psychiat.* 53: 329, 1945.

²⁹³⁶ PAGNIEZ, P., VALLIERA RADOT, P., and NAST, A. *Presse méd.* 27: 172, 1919.

²⁹³⁷ BROWN, T. R. *J. A. M. A.* 77: 1386, 1921.

²⁹³⁸ VAUGHAN, W. T. *ibid.* 88: 1385, 1927.

²⁹³⁹ ROWE, A. H. *ibid.* 99: 912, 1932.

²⁹⁴⁰ LIECHER, L. E. *Ann. Int. Med.* 20: 752, 1944.

²⁹⁴¹ TUFT, L. *Pennsylvania M. J.* 39: 162, 1933.

²⁹⁴² HILL, L. W. *Bull. New York Acad. Med.* 16: 395, 1940.

²⁹⁴³ CONWELL, D. A., and KURTH, C. J. *J. Kansas M. Soc.* 41: 415, 1940.

cucumbers, beef, and oranges Unger²⁹⁴⁴ was able to bring on migraine by feeding his patient cauliflower, broccoli, Brussels sprouts, asparagus, and curly endive, furthermore, attacks of migraine were deliberately induced by injections of extracts of these foods

Among animal foods eggs seem to be of special importance (Vaughan,²⁹⁷³ Urbach) Cases due to milk have been described by Wolf and Unger²⁹⁴⁵ and Randolph⁷³⁶ In the latter's patient, severe attacks were induced by merely working in a formula room and by an intradermal skin test

Gerson considered table salt as an important allergen The present writers, however, are of the opinion that salt itself is rarely the allergen, the elimination of table salt, as well as of sugar (Foldes and Wagner Jauregg), is effective because the subsequent dehydration tends to prevent cerebral edema This assumption is supported by the fact that a salt and sugar free diet does not control the migraine attacks until considerable time has passed, on the other hand, when the allergen is eliminated, they stop within one or two days

Next in order for consideration are the inhalant allergens, especially those that have distinct odors (roses, violets, certain perfumes, turpentine, naphthalene, tar, etc) Other inhalants include insect powders and sprays (Goltman²⁹²⁶), house dust (Vaughan²¹), and the emanations from intestinal worms, which may cause migraine in laboratory workers Goltman's investigations are of importance in showing that inhaled substances are rapidly absorbed, e.g. phenolsulfonphthalein introduced into the accessory sinuses was demonstrable in the urine ten minutes later Service¹²⁰⁹ reported migraine as a delayed reaction to penicillin injections

Kaemmerer²⁰⁸ pointed out that migraine can occasionally be caused by bacterial allergy He reported cure of a case by removal of a granuloma of a tooth

According to Lichtwitz,⁵⁹¹ endogenous allergens play a more important rôle in the pathogenesis of migraine than do exogenous allergens This theory has since found confirmation—at least as regards premenstrually occurring migraine—in successful deallergiza-

tion by means of autogenous serum withdrawn before the menstrual period (Cameron,⁶³⁸ Urbach²⁹⁷⁷) Moffat²⁹⁴⁸ felt that the good results obtained with small doses of the gonadotropic factor of pregnancy urine in his series of patients with menstrual migraine was attributable to desensitization to this substance The writers are of the opinion that many cases in which there are regular attacks of migraine following constipation, other in testinal disturbances, and physical as well as mental fatigue, can be similarly attributed to endogenous allergens

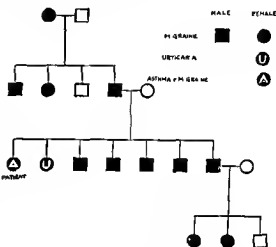


FIG 392 GENEALOGIC CHART SHOWING INCIDENCE OF MIGRAINE IN FOUR GENERATIONS

In addition to the actual allergens, predisposing factors (see p 52) are also of great importance in migraine Of these, heredity is undoubtedly the most decisive The literature abounds with family trees in which migraine is seen in four and even more generations, and it must be noted that in the great majority of instances the affliction is transmitted through the females FIGURE 392 represents the genealogy of one of the writers' own patients Balyeat²⁵¹⁴ published numerous examples that show how frequently other allergic diseases are found in the families of migraine patients Hanhart²⁹⁴⁷ contributed a series of thirty-five family trees with a high incidence of migraine and pointed out that the members of these families were afflicted

²⁹⁴⁴ UNGER L J Allergy 12 197 1931

²⁹⁴⁵ WOLF A A and UNGER L Ann Int Med 20 825 1944

²⁹⁴⁸ MOFFAT W M JAMA 108 612 1937

²⁹⁴⁷ HANHART E Deutsche med Wchnschr 62 2006 1936

with a great variety of allergic diseases. Examining a series of 100 children of parents with migraine, Bray⁷⁹ found that 82 per cent were allergic, and that of 209 close relatives, 112 suffered from migraine, 65 from asthma, 11 from hay fever, 11 from dermatitis, 6 from epilepsy, and 4 from urticaria. In 73 per cent of these cases, only one parent had migraine (in 57 per cent the mother, in 16 per cent the father). In 22 per cent of the cases both parents had been afflicted, and in 5 per cent there was a history of migraine in a blood relative. Bray makes the comment that he found an unusually high incidence of migraine among the mothers and aunts of asthmatic children.

In a series of 452 cases of asthma, the senior author⁸⁴ elicited a family history of migraine in the close relatives of 23 per cent of the female and in 13 per cent of the male asthmatics. It is worthy of note that we⁸² have observed the same high incidence of migraine in the parents and siblings of urticaria patients, and here, too, much more frequently among female than among male cases. These figures surely seem to indicate the existence of an intimate relationship between asthma and migraine, as well as between urticaria and migraine.

From the point of view of heredity, there seem to be two types of migraine: one in which the migraine is the principal disease, transmitted from generation to generation according to the mendelian law, and chiefly through the female, as a dominant but not sex-linked characteristic; and the other, a type in which the migraine appears alternately with other allergic manifestations in allergic individuals and their families. This frequency of allergic symptoms, both in the patient and in his immediate family, is another important indication of the allergic origin of certain cases of migraine.

In the light of our present understanding, certain generally recognized predisposing factors—e.g., physical and mental fatigue, emotional upsets, endocrine disturbances, toxic conditions—may often be contributory factors in migraine. However, they may in some cases even be responsible for allergization by inducing the formation of endogenous substances that may be allergenic per se (endogenous allergens).

c) SYMPTOMATOLOGY

From the clinical point of view, four distinct stages can be observed in migraine: the prodromal state, the aura, the attack, and the postmigrainous symptoms.

First of all, it must be said that the individual case does not necessarily have all the symptoms, although most of them are usually present. The same patient may show different symptoms in different attacks. Sometimes, as will be shown below, one stage or another may fail to appear. Finally, it should be noted that the clinical picture in children varies considerably from that in adults.

In adults, the *prodromal* period is introduced either by a mild to severe feeling of depression, or by physical and mental hyperactivity. Many patients mention having enjoyed abnormally sound sleep during the night preceding the attack. There have been many reports of abnormal hunger on the day before the attack.

The *aura* is especially characteristic of migraine. Immediately before or early in the course of the attack, the patients have one or more of the following symptoms. Most commonly there is a visual aura, in the form of scintillating scotomata, blurring of vision, a sensation of zigzag "lights," and hemianopsia; second in order of frequency are photophobia and vertigo, often mild but sometimes very pronounced. Very frequently there are sensory disturbances in the form of paresthesias, usually of the extremities, and described as feelings of tingling or numbness. Olfactory symptoms, such as hallucinations of smell and taste, are not infrequently found. Auditory symptoms (tinnitus, temporary diminution of hearing) and motor disturbances (transient paresis of the extremities, motor aphasia, drooping of the eyelid of the affected side) are rarely observed. Finally, vasomotor disturbances are often encountered (pallor or congestive reddening of the face prior to and during the attack, sweating).

About one to three hours after the beginning of the sensory, motor, or vasomotor symptoms, the severe *headache* starts; it is confined to one side of the head in about two-thirds of all cases. In many cases, the same side is invariably affected, while in others the laterality may differ or alternate in successive attacks.

Some patients awaken in the middle of an attack, having passed through the aural stage in their sleep under these circumstances they generally complain of having had unusually terrifying, nightmarish dreams. The attack itself is not only painful, but is accompanied by a feeling of weakness and extreme depression. Many patients become mentally confused, or at the very least their thinking is retarded and their memories impaired. At first the pain is localized in the temporal or frontal region in the vertex, or in the occipital area but may then become generalized. The duration of the attack may be anywhere from two hours to two days the average is approximately ten hours (Baljeat²⁵⁴). The intervals between attacks also vary considerably, but are usually fairly constant in the individual case. Onset of the pain is commonly accompanied by nausea, less often by vomiting. Occasionally, abdominal pain dominates the picture to such an extent that it gives rise to errors in diagnosis. Kelling,²⁵⁵ Iodor and Kunos,²⁵⁶ Bray⁷⁹ and others have reported the appearance, during attacks of migraine, of symptoms clinically typical of gallbladder disease or appendicitis, with the result that unnecessary operations were performed. A case of Urbach's illustrating this situation was reported by Bauer.²¹⁰ During a migraine attack the patient suffered such violent pain in the right side of the epigastrium that a laparotomy was performed. No stones were revealed, but the sphincter of Oddi was found to be obstructed by an acute edema, probably of allergic nature. These cases are most probably to be interpreted as the result of vascular spasm, and differ from the cerebral cramps of migraine only with respect to their localization. Therefore, the designation *abdominal or visceral migraine* seems most appropriate.

It happens occasionally that an attack of migraine does not complete its full course. That is, it appears only in the form of a so-called "migrainous equivalent" (scintillating scotomata, hemianopsia, aphasia, abdominal pain, and the like).

As mentioned, the symptoms presented by children are rather unlike those of adults. In children the prodromal manifestations are

fatigue, loss of appetite, abdominal discomfort, constipation, and, fairly often, slightly or markedly elevated temperature. Visual phenomena are almost totally lacking in the aura. The attack is nearly always accompanied by ketotic vomiting followed by recurrent very painful intestinal colic, with small bowel movements. These abdominal symptoms may be so pronounced that they completely dominate the picture, with the result that the accompanying headache is overlooked. Furthermore, it is important to note that in young children migraine may manifest itself exclusively as so-called cyclic vomiting. However, according to Bray,⁷⁹ this can be differentiated from "true" cyclic vomiting in that the latter condition responds to administration of glucose and also characteristically is accompanied by a high acetone content in the urine and in the breath. Vaughan²⁵⁷ is of the opinion that cyclic vomiting in childhood migraine is attributable to a cerebral edema.

In both children and adults, the attacks are followed by a *postmigrainous stage* after the headache and the gastro-intestinal symptoms have subsided, the patient is often completely exhausted and usually very sleepy. In addition, he feels a generalized body soreness, as though he had been beaten. Finally, there is often polyuria and a discharge of thin mucus from the nose. Instead of having a strong desire to sleep, as adults have, children are often restless and unable to sleep during this stage, fits of crying have often been observed.

d) DIAGNOSIS

Not every headache—even of demonstrably allergic origin—should necessarily be regarded as migraine (Rinkel²⁵⁸). The diagnosis of migraine is to be made only when the headaches appear in sudden violent attacks accompanied by certain manifestations of irritation of the cerebral cortex, such as scintillating scotomata, hemianopsia, and parestheses. On the other hand, the fact that the symptoms begin suddenly and violently does not in itself conclusively prove that the condition is migraine, for these characteristics are also observed in the "histaminic cephalalgia" of Horton.²⁵⁹ Von Storch²⁶⁰ states that of the four cardinal symptoms of migraine—re-

current hemicranial headache, visual disturbances, gastro-intestinal symptoms, and hereditary migraine diathesis—it is necessary that at least the first of these and one other be present before a diagnosis of migraine can be considered, and that three should be present before it can be certain. To this many authorities would add relief from ergotamine tartrate administered early in the attack as at least suggestively diagnostic, since this drug rarely influences headaches of other origins.

Before a definite diagnosis of migraine is made, the following possible causes of headache must first be excluded: eyestrain or other eye conditions; nasal obstruction or paranasal sinusitis, nasal or upper respiratory allergy, neurologic conditions such as trigeminal, glossopharyngeal, and other neuralgias, brain tumor, and cerebral trauma; cardiovascular diseases such as hypertension, nephritis, cervical arthritis; myalgia and myositis of the muscles of the cranial, cervical, and pharyngeal muscles, primary and secondary fibrositis, pelvic disorders; infections, including syphilis, and psychogenic disorders (conversion hysteria). Aside from the aforementioned features, one of the outstanding symptoms of migraine is its periodicity. Headaches due to other causes are generally of more protracted and constant type.

Migraine must be differentiated from "histaminic cephalalgia," sometimes known as "erythrocephalgia." Horton²⁷¹ contributed a splendid study in which he clearly drew the line between this group of vascular headaches and migraine. He pointed out that clinically, and particularly in its excellent response to histamine therapy, the former condition can be readily differentiated from migraine, and that subcutaneous injection of 0.1 mg. of histamine can evoke headaches in patients subject to the histaminic type of attack. Histaminic cephalalgia is characterized by unilateral headache, usually beginning in the later decades of life and more common in males than in females. The laterality of the pain tends to be constant in a given patient. It is of short duration, generally lasting less than an hour. It commences and often terminates suddenly. These attacks are almost never accompanied by visual disturbances or by gastro-intestinal

symptoms. Swanson,²⁵⁰ however, described a case with constriction of the visual field on the homolateral side, as well as severe nausea and vomiting, and the junior author has seen the latter symptoms in mild degree in two cases. The headache is associated with profuse watering and congestion of the eye, rhinorrhea, increased surface temperature, and frequently with swelling of the temporal vessels, all on the involved side of the head only. There is no hereditary background for the occurrence of these attacks. No specific allergy has been demonstrated as being related to this syndrome. On the basis of recent publications by J. R. Williams²⁵¹ and Wilhelm,²⁵² Forman²⁵³ has tabulated the differential signs and symptoms of histaminic cephalalgia and migraine (Table 62). The former type of headache responds rather promptly to subcutaneous injections of histamine diphosphate, given twice daily for approximately from ten days to three weeks.*

H. L. Williams¹⁹⁷ has defined a syndrome of myalgia of the head, which appears in the third decade of life or later, probably as a manifestation of physical allergy, and which must also be differentiated from migraine. The symptoms are precipitated by exposure to physical stimuli such as drafts, changes in temperature, changes in atmospheric pressure with approaching storms, emotional stimuli, and anxiety states. There is circumscribed tenderness of the origins, attachments, or stiffened portions of the belly of certain muscles, and while more than one may be affected, the involvement is usually unilateral. The involved muscles may include the trapezius, sternocleidomastoid, splenius capitis, temporalis, occipitofrontalis, or any of the pharyngeal muscles. The pain is of the deep or smooth type and the distribution of its referral is independent of that of the spinal

²⁵⁰ SWANSON, I. W. *Ibid.* 15: 144, 1944.

²⁵¹ WILLIAMS, J. R., Jr. *North Carolina M. J.* 6: 239, 1945.

²⁵² WILHELM, S. *Rocky Mountain M. J.*, May 1945, p. 360.

²⁵³ FORMAN, J. *Letters, Internat. Corr. Club of Allergy*, Series 8, 62, 1945.

* Horton recommends the following schedule, using a 1 cc ampule containing 0.275 mg. of histamine diphosphate, equivalent to 0.1 mg. of histamine base: an initial subcutaneous dose of 0.25 cc., with increase of the dose successively every second day by 0.05 cc., provided there are no untoward effects, such as severe flushes and headaches, until a total dose of 1 cc. is reached; thereafter, maintenance doses of 1 cc. each. A great many cases cannot tolerate more than one-tenth to one-fifth of the dosage cited.

roots The pain may be reproduced by pressure on the tender spots or by injection of histamine or hypertonic saline solution into the involved part of the muscle, and it may be abolished by infiltration of procaine into the

The allergic nature of migraine is not necessarily proved by cessation of the attacks after a systematic change in the patient's diet To make the diagnosis of an underlying allergy certain, the attacks must recur after admin-

TABLE 62 — *Differential Diagnosis of Chronic Vascular Headaches (after Torman²¹⁸³)*

Sign or Symptom	Histaminic Cephalalgia	Migraine
HISTORY		
Onset	More often later in life	Younger group
Mode of onset	Acute in onset	Preceded by <i>aura</i>
Time of onset	Often at night before retiring	Any time day or night
Duration	Short attacks with abrupt termination	Hours to days
Location	Almost always unilateral	Unilateral or whole head
Nausea and vomiting	No nausea or vomiting	Severe nausea and vomiting
Visual disturbances	None	Present before and during
Familial history	None	Familial history (85-90%)
Allergic history	None or coincidental	Usually found
Relation to menstruation	None	Often
PHYSICAL FINDINGS		
Flushing of affected side	Usually present	Only occasionally
Lacrimation	On affected side in average case	None
Rhinorrhea on affected side	Present	None
Increased skin temperature	On affected side	None
Tenderness over external carotid artery or temporal on affected side	Occasionally present	Present
Relief from sitting up or standing	Relief	No relief
Tenderness of scalp afterwards	Usual	None
LABORATORY FINDINGS		
Leucocyte count	Normal	Eosinophilia (> 16%) temporary in large percentage of cases
TREATMENT		
Epinephrine	Prompt relief	No effect
Histamine	Will induce attack and gives excellent result with the desensitization regimen	Will not induce an attack but may help in non specific way
Ergotamine tartrate	No effect	Best available treatment will stop attack

latter, but not into the region of reference No structural changes have been demonstrated In certain cases, evidences of vasodilatation, mucoid nasal secretion, tinnitus, vertigo, and the like are present on the homolateral side during the attack The recommended treatment is niacin (nicotinic acid), at first by injection and later by mouth

istration of certain foods or exposure to certain inhalants, and must fail to appear on avoidance of the given agents, or when propeptans have been properly administered

In practice, one of the following procedures is recommended for identifying the allergenic foods

(1) A strict elimination diet, on the basis

of evidence supplied by the patient's history. If the patient remains free of symptoms for some time on this diet, he is then given a large quantity of the suspected food each morning for two days. If this precipitates an attack of migraine, it is evident which food or foods are responsible.

(2) Strict adherence to a propeptan diet (see p. 190). If no migraine attacks appear after several days of this regimen, a certain propeptan—e.g., wheat or milk—is omitted, but the corresponding food is given. Subsequent appearance of the symptoms definitely indicates the offending food.

Inhalant allergens are best identified by appropriate nasal or bronchial tests.

The results of scratch and intracutaneous tests are to be evaluated with considerable caution. For, as is well known, the elimination of a substance or substances producing positive reactions on skin testing is often therapeutically ineffective; on the other hand, allergens that actually elicit attacks of migraine not infrequently fail to yield positive skin reactions. This does not mean that skin tests may not be performed; but it must always be remembered that the results are to be considered specific only in so far as they coincide with clinical observations.

e) TREATMENT

There are three aspects to the management of migraine: the prophylactic, the etiologic, and the symptomatic, the latter comprising measures employed both during and between attacks.

Prophylaxis

The only truly effective prophylactic measure would be to persuade an individual suffering from migraine not to marry anyone suffering from the same affliction, or at least not to have any children. However, since migraine patients are quite often talented and highly intelligent personalities, such advice would seem to be improper as far as the interests of the community are concerned. When the causative allergic factors—whether foods or inhalants—can be identified, and when hypersensitization is impossible, the patient should carefully avoid exposure to the allergenic agents.

Furthermore, all predisposing factors should be eliminated, if possible. It must be borne in mind that physical and mental fatigue, and also emotional and depressed states, definitely play important rôles in this respect. The patient must be advised to pursue an easy, smooth tenor of life, physically and emotionally (Unfortunately such advice is not so easily followed in practice.) Furthermore, the possibility of eyestrain should be carefully considered and any existing condition corrected. In addition, elimination of all foci of infection should be attempted.

Etiologic Treatment

When one or more foods have been definitely identified as responsible for the attacks, and when these food items are such that they cannot readily be eliminated from the normal diet, deallergization by oral methods (ingestion of minute quantities of the foods in increasing amounts, according to the technic described on p. 301), or species-specific propeptan therapy (p. 217) is indicated.

The following case may serve as an illustration.

A patient 42 years old had been suffering from migraine attacks ever since his early youth, his grandmother, mother, sister and his one child, now 13 years of age, were similarly affected. The patient's family history also included other allergic diseases. His father suffered from urticaria attributable to eating of crabmeat. His brother had dermatitis due to woolen shirts and stockings. Since the patient claimed that he always had migraine after eating chocolate, oral experiments were made with cocoa and with various forms of chocolate. Regularly, some four hours later, the patient responded with severe migraine on the right side, uncontrollable yawning, and a noticeable swelling of the right upper eyelid. These manifestations subsided after injections of epinephrine or caffeine. Preliminary administration of 10 tablets of cocoa propeptan were effective in preventing onset of the migraine. It was possible rapidly to reduce the propeptan dose during the next few days. Finally, within sixteen days, the patient tolerated chocolate perfectly.

Von Eiselsberg²⁹⁴ reported similar good results with propeptan therapy in migraine.

When inhalant allergens are known to be the responsible agents, specific hyposensitization (p. 203) may be attempted.

In cases of menstrual migraine, Cameron⁵³³ and the writers²³⁷ have had gratifying results

²⁹⁴ EISELSBERG, K. P. von. *Wien. klin. Wchnschr.* 45: 332, 1932.

with desensitization by means of the patient's own serum

Technic The blood is withdrawn two or three days before the beginning of the menstrual period when the first slight headaches are beginning to be felt. The blood is centrifuged and the serum preserved in sterile ampules. Merthiolate (0.01 per cent) is added. When the menstrual period is over 0.2 cc is injected intracutaneously every other day until the beginning of the next menstruation. Four injections are given in the same skin site, then a new site is chosen for the next four and so on. After two or three of these series the premenstrual headaches are usually greatly alleviated and sometimes entirely eliminated.

In other cases of menstrual migraine, good results can be achieved with appropriate hormonal substitution therapy (ovarian, corpus luteum, and pituitary extract). According to O'Sullivan²⁹⁵ proper endocrine therapy depends on the recognition of the underlying pathologic process: (1) for women with headaches definitely related to the menstrual period and those of the Lorain Levi pituitary type, placental estrogenic substance, (2) for women whose migraine is associated with the menopause or with previous oophorectomy or hypo ovarianism alpha estradiol benzoate, (3) for those with intense exhaustion just before attacks and with low basal metabolic rates, thyroid, even in underweight patients, and (4) for patients of the "pituitary type," pituitary extract. Glass²⁹⁶ also obtained good results with estrogen therapy in patients with menstrual migraine who had a low estrogen excretion and high gonadotropin excretion.

When, in a given case, the personal or family history suggests that the migraine is of allergic nature—though the allergen cannot be demonstrated—metaspecific desensitization methods are indicated. For this purpose peptone, tuberculin, typhoid vaccine, and autohemotherapy are most suitable (See chap XII for details).

Symptomatic Treatment of the Acute Attack

While an attack is in progress, the patient should be down, with an ice cap on his head, in a darkened room. Relief is often afforded by a colonic irrigation or a high enema. Medicinal treatment should be instituted as promptly as possible. Numerous clinical and

experimental investigations of the past few years (Lennox and von Storch) have highlighted the efficacy of *ergotamine tartrate* (marketed under the name *gynergen*) in migrainous headache. In general, the intramuscular route is recommended, with a dose of 0.5 to 1 cc (containing 0.25 to 0.5 mg), this may be repeated in one hour if necessary. The optimal success with the smallest dose is achieved in the early stages of the attack—namely, at the onset of the first prodromal symptoms. Relief from cephalalgia, and also from visual symptoms, paresthesia, photophobia and abdominal pain will occur within from fifteen to thirty minutes after intravenous injection, within from forty five to ninety minutes after treatment by the subcutaneous route, and in from two to three hours following oral administration. The symptoms, once they have been aborted, rarely return. Vomiting, nausea, weakness, and prostration, on the other hand, do not respond to ergotamine tartrate, least of all when the drug is administered at the height of the attack. Oral treatment should be reserved for mild forms not associated with emesis. Three tablets (3 mg), taken as early in the attack as possible, bring relief in some 60 to 90 per cent of these cases. Some authorities advocate repeated doses, up to a total of 10 or 12 mg. The drug is effective when the tablets are allowed to dissolve under the tongue. When vomiting or nausea has become established, medication by mouth is impractical. It should be noted that ergotamine is largely ineffectual in headaches of other than migrainous origin.

When *gynergen* has once proved effective in a given case, the patient will respond favorably to the drug in all subsequent attacks, and should be taught to give himself the injection just as soon as the headache commences or when prodromal symptoms appear. In mild cases such patients should try to abort the attack by promptly taking 2 tablets of 1 mg each.

Some patients may experience muscle pains, slight transitory dyspnea, nausea, and vomiting as after effects of the drug. These symptoms can be relieved almost immediately by intravenous injection of 10 cc of calcium gluconate, and/or an injection of 1/100 gram of atropine sulfate. Other untoward effects include stiffness of the joints, a sense of constriction in the

²⁹⁵O'SULLIVAN, N. E. *Endocrinology* 21: 414, 1939.

²⁹⁶GLASS, S. J. *ibid.* 20: 333, 1936.

throat, heaviness of the chest, and burning and tingling of the fingers and toes. Ergotamine is contraindicated in pregnancy, thyrotoxicosis, coronary and hepatic disease, acute infections, and hypovitaminosis, especially C-deficiency. In patients with peripheral obliterative vascular disease it should be used with great caution, if at all. Carter²⁷⁰⁷ reported a case with cardiac manifestations after a single injection, attributable to individual sensitivity.

A decreased susceptibility to migraine cannot be achieved even by prolonged treatment with gynergen. This fact, and the danger of ergotism following more or less continuous administration of the drug, are reasons for restricting its use to actual attacks. As an exception to this rule, however, gynergen may be administered as a prophylactic, shortly before menstruation, in cases of menstrual migraine.

The mechanism of the action of gynergen has not as yet been thoroughly elucidated. Generally speaking, there are now two schools of thought on the subject. The first believes that the effect of gynergen is due to its stimulating action on the smooth muscle of the vessels of the brain. Experimental studies, carried out chiefly by Graham and Wolff,²⁷⁰⁹ give strong support to this theory. The second school attributes the effect of gynergen to its specific sympathico-depressant properties, which serve to change the sympathetic tonus and relieve the vasomotor disturbances of the vessels of the brain. In the latter respect the drug's action is the reverse of that of epinephrine. Von Storch points out that, in contrast to epinephrine, gynergen has a vasoconstrictive effect of long duration, which might perhaps explain the specific action of the drug.

A new derivative of ergotamine, dihydroergotamine (D.H.E.-45), is claimed to be at least as effective, and to be much more free of such side effects as nausea, uterine cramps, and ergotism (Horton et al.²⁷⁰⁸ and Hartman²⁷⁰³).

Another remedy that has in the past few years proved to be of some value is *acetyl-*

choline. According to Goldkuhl,²⁹²¹ gynergen is helpful in the treatment of severe, acute attacks of migraine only when the patient presents pallor during the attack (white migraine), while those individuals whose faces become congested (red migraine) are relieved only by intramuscular injection of acetylcholine. The recommended dose of acetylcholine is from 0.1 to 0.3 Gm. (1½ to 5 grains) injected intramuscularly, and repeated at thirty- to sixty-minute intervals if necessary.

Lumière²⁹⁰² has recommended intravenous injections of 50 per cent *magnesium sulfate* twice weekly, the first dose to be 2 cc., the second 5 cc. This treatment necessitates certain precautionary measures. The injections must be given very slowly, in fractions of a cubic centimeter. Each is promptly followed by an intense flush of short duration. As soon as this has subsided, injection may be resumed and another cubic centimeter administered. Pines,²⁹⁰¹ Schick, and others reported good results with this procedure.

Alvarez, Boothby, and others recommend breathing of pure oxygen for at least two hours, preferably through a BLB mask. One can first try the effect of oxygen by giving it with a basal metabolism apparatus. If this works well, the patient should have a tank, reducing valve, and mask at home. There is no danger or discomfort in this treatment.

Analgesics such as acetylsalicylic acid (0.3 to 1.0 Gm., or 5 to 15 grains), antipyrine, or acetphenetidin (0.3 to 0.6 Gm., or 5 to 10 grains), given at intervals of from two to four hours, may sometimes be of value, when taken very early in the attack.

Caffeine sodiobenzoate will give quick relief in some cases. It is most effective when given intramuscularly (since subcutaneous administration is very painful) in amounts of 0.25 Gm. (4 grains). Where this is impossible, it may be taken by mouth.

Amphetamine sulfate (benzedrine sulfate), because of its prolonged vasoconstrictive and concomitant pressor effects, was advocated by J. S. Gottlieb²⁹⁰² in intravenous doses of 3 to 20 mg. Those patients responding to injection were advised to take 10 to 40 mg. of the drug

²⁷⁰⁷ CARTER, J. B. J.A.M.A. 114: 2298, 1936

²⁷⁰⁸ HORTON, B. T., PETERS, G. A., and BUCHHEITEL, L. S. Proc. Staff Meet., Mayo Clin. 20: 241, 1945

²⁷⁰⁹ HARTMAN, M. M. Ann. Allergy 3: 440, 1945

²⁹⁰¹ LUMIÈRE, A., and MEYER, P. Compt. rend. Soc. de biol. 115: 534, 1934

²⁹⁰² PINES, N. Lancet 1: 577, 1933

²⁹⁰³ GOTTLIEB, J. S. Am. J. M. Sc. 284: 553, 1942

orally at the beginning of an attack. In cases with frequent paroxysms oral divided doses were employed as a prophylactic agent.

Thiamin chloride in intramuscular injections of 120 to 180 mg terminated the headache in one to three hours in 70 per cent of the attacks according to Palmer.¹⁹⁶³

Since induced hypoglycemia is thought to be antispasmodic and antagonistic to sympathetic activity, Tillim¹⁹⁶⁴ employed *insulin* in 2 cases of migraine and achieved prompt and prolonged relief. The dosage required varied from time to time being determined by the clinical manifestations of hunger, thirst, diaphoresis and somnolence. It was not necessary to induce coma. Intravenous administration of the insulin produced a more rapid response.

Sedatives are often necessary. In case of nausea a rectal suppository containing from 0.1 to 0.2 Gm (1 1/2 to 3 grains) of nembutal is often helpful. Phenobarbital and sodium phenobarbital (0.015 to 0.030 Gm or 1/4 to 1/2 grain) are recommended. Injection is often inevitable.

Narcotics, such as morphine, should be given only as a last resort in very severe attacks. However, Trowbridge, von Storch, and Moore¹⁹⁶⁵ state that morphine is completely effective in 59 per cent of patients using it as compared to 80 per cent with ergotamine tartrate.

Symptomatic Treatment Between Attacks

Many drugs, hormonal preparations and even surgical therapy have been advocated to control the mechanisms leading to migraine. However, the very fact that new medications are constantly being introduced is a reflection of the basic ineffectiveness of most. Yet certain cases can be favorably influenced by one method or another when specific therapy fails or is ineffectual. Nearly all depend for their effect on their action on the vascular mechanisms of the body.

A series of intravenous injections of 1 mg of *histamine* (2.75 mg of histamine acid phosphate) was recommended by Butler and

Thomas.¹⁹⁴⁵ The drug must be well diluted with saline and injected very slowly. The present authors have not found this method to be as effective as claimed and not without danger.

According to Atkinson¹⁹²² it is necessary to distinguish between the cases due to histamine sensitivity and manifesting primary vasodilatation and those with primary vasoconstriction (see above). For the former a slow histamine desensitization is suggested, never exceeding a dose of 0.5 mg given subcutaneously. The maximum dose is administered at weekly intervals for four weeks and a second or even third course may be required some months later. For the latter type of case *nicotinic acid* (not the amide) is advocated, given by intravenous or intramuscular injection in increasing dosage and later by mouth (Atkinson¹⁹⁴⁶). At the same time general management including a high protein low-carbohydrate diet should not be overlooked. He warns that ergotamine tartrate should be used with discretion since it does nothing to prevent and may even favor recurrences and since logical treatment demands a vasodilator and not a vasoconstrictor according to his theory.

Favorable results in migraine with a course of injections of *histamine azoprotein complex* (Hapamine) have been reported by Warren and Findley.¹⁹⁴⁰

Thiamin hydrochloride in daily intramuscular injections of 30 to 100 mg over a period of one to two months and longer in very severe cases was administered by Palmer¹⁹⁶³ on the basis that migraine may be due to a hypothetical toxin formed as the product of metabolism which has been deranged by the absence of some essential enzyme. At the same time vitamin B complex was administered by mouth. As soon as a reduction in the number of attacks was noted the interval between injections was gradually lengthened. About one half the patients were completely relieved, others noted a reduction in the severity and frequency of attacks and some failed to respond. Others have recommended thiamin hydrochloride several times a day by mouth, along with niacin (nicotinic acid).

Brown¹⁹⁶⁷ found that migraine could be

¹⁹⁶³ PALMER, H. D. Arch. Neurol. & Psychiat. 45: 368, 1941.

¹⁹⁶⁴ TILLIM, S. J. Ann. Int. Med. 29: 597, 1944.

¹⁹⁶⁵ TROWBRIDGE, L. S., VON STORCH, T. J. C. and MOORE, M. New England J. Med. 227: 699, 1947.

¹⁹²² ATKINSON, M. Ann. Int. Med. 21: 990, 1944.

¹⁹⁴⁶ BROWN, J. A. Brit. M. J. 2: 201, 1943.

controlled by 1.3 Gm. (20 gr.) of *urea* taken in water three times a day for one week, twice daily for one week, and then once daily for an indefinite period. He attributed its effect to the diuresis produced.

Assuming that migraine is perhaps due to uncompensated fluctuations in the effective arterial blood volume, Pfeiffer, Dreisbach, and Roby²⁹³ employed a salt mixture of *calcium lactate* and *potassium chloride* in a proportion of 1:3 molar equivalents (308 Gm and 225 Gm, respectively) in order to produce a temporary increase in blood volume. Given in this proportion, neither drug has diuretic effect. Capsules containing 0.65 Gm. (10 grains) of the mixture along with 1 per cent of added nicotinamide were given in increasing dosage up to 3 capsules a day with rather satisfactory results.

Based on the action of prostigmine in liberating acetylcholine and preventing its destruction by acetylcholine esterase, Pelnar and Aibel²⁹⁴ thought that oral administration of *prostigmine bromide* in increasing doses might produce a desensitization to acetylcholine. One 15 mg. tablet is dissolved in one ounce of water, and given in a dose of 1 drop three times a day, increasing each dose by 1 drop until 30 drops are reached. This dose is taken daily for one week and then every other day until the patient is free from symptoms. The authors claim that all periodic headaches, whether migrainous or of the histamine type, were relieved to a great extent. Lieder,²⁹⁵ however, obtained no results with prostigmine.

The employment of *hormones* for the specific treatment of underlying endocrinopathies is discussed above. Other investigators, however, have given them in unselected cases. Dunn²⁹⁶ found that a series of two to four injections of estradiol benzoate (progynon B) in doses of 6,000 to 10,000 R. U. at intervals of two to four days usually aborted, relieved, or controlled the recurring attacks and lessened their frequency in 9 males. He also advocated a single dose as soon as possible after the onset of visual symptoms. Moffat²⁹⁷ and Leyton²⁹⁸ used chorionic gonadotropin with

favorable results in women in whom there was no relationship between the headaches and menstruation.

Other drugs which have been recommended include injections of *pentamethylenetetrazol* (Leroy²⁹⁹) and *chondroitin* by mouth (Drewyer²⁹²).

Of the *operative procedures* reported, von Storch³⁰⁰ advocated interruption of the periarthral neural pathway by ligation and section of the middle meningeal artery, and Nadler³⁰¹ of one or both temporal arteries in selected cases. Obviously, such intervention will be reserved for certain severe, intractable cases. Recently, Patzer, Derbes, and Engelhardt³⁰² employed periarthral infiltration with 0.1 per cent eucupine (isoamylhydropyrene), a local anesthetic of prolonged action, in 1 per cent procaine solution. The injections are given in the vicinity of the superficial temporal artery of the involved side, and often it is necessary to inject subsidiary painful points discovered by palpation. The majority of patients had immediate relief, and even the "failures" noted decreased frequency of attacks as a rule.

Finally, the effectiveness of certain *diets* must be mentioned. Overeating and excessive water-drinking should be interdicted in all cases. Excellent results have frequently been achieved with the Gerson diet when strictly adhered to for some time. This diet is not only practically salt-free but also protein-poor. Similarly, good results have been obtained with the carbohydrate-poor diet (Foldes; Wagner-Jauregg). Both of these diets have a dehydrating action. The ketogenic (carbohydrate-poor and fat rich) diet of Boborka is worth mentioning. The beneficial effect of this last diet is often limited by the fact that it is so unappealing to the taste of the patient. We in our own cases have frequently observed excellent results from a carbohydrate- and salt-poor diet. Since adherence to such a regimen makes rather strenuous demands on the patient's will power, it is advisable to begin with a carbohydrate-poor diet main-

²⁹³ LEROY, A. *J. belge de neurol. et de psychiat.* 39: 135, 1939.
(Abstr. JAMA 114 833, 1940)

²⁹² DREWYER, G. E. *J. Michigan M. Soc.* 39 453, 1940.

²⁹¹ NADLER, S. B. *JAMA* 129: 334, 1943.

²⁹⁰ PATZER, R., DERBES, V., and ENGELHARDT, H. *Arch. Surg.* 59 296, 1945.

²⁹⁴ PFEIFFER, C., DREISBACH, R. H., and ROBY, C. C. *J. Lab. & Clin. Med.* 29: 709, 1944.

²⁹⁶ DUNN, C. W. *Delaware State M. J.* 13 89, 1941.

²⁹⁵ LEYTON, N. *Lancet* 1: 458, 1942.

tained for the first four weeks, and then if the result is not satisfactory, to substitute a salt poor regimen for the next two months. Finally, a salt and carbohydrate poor diet is instituted only if the previous diet alone does not produce full results. The following instructions are given to the patient for strict enforcement of this diet.

LOW SALT, LOW CARBOHYDRATE DIET

- 1 No salt or sugar is to be used in cooking or at the table
- 2 No canned soups, meats or vegetables are to be eaten
- 3 The following foods are to be completely eliminated
 - Because of salt content
 - a) sausage, ham, all salted, smoked or spiced meats
 - b) smoked and salted fish
 - c) seafood (clams, oysters, lobster, etc.)
 - d) cheese
 - e) pickles
 - Because of carbohydrate content
 - f) honey, molasses, syrups
 - g) candy, cocoa, chocolate
 - h) jelly, jam, marmalade
 - i) ice cream, cakes, soft drinks
 - j) pies, cookies
 - k) dried fruits, puddings, tapioca
 - l) macaroni, noodles, cereals
- 4 The following foods should be eaten in limited amounts
 - a) white potatoes, corn, dried beans, parsnips (one small serving daily)
 - b) bread (white, whole wheat or rye) baked without salt or toast made from such bread (one slice at each meal) or three unsalted crackers
 - c) milk or buttermilk (not more than 8 ounces daily)
 - d) beets, Brussels sprouts, mushrooms, peas, spinach
 - e) custard (only occasionally)
- 5 The following foods may be eaten freely
 - a) all meats, poultry and fish except as noted in 3a, b, c
 - b) eggs in any style
 - c) all soups made without thickening and without salt
 - d) all vegetables except sweet potatoes and those mentioned in 4d
 - e) all unsweetened fruit juices, all fresh or unsweetened cooked fruits except bananas, grapes, cantaloupes, watermelon
 - f) lettuce and salads
 - g) sweet (unsalted) butter, cream, coffee, tea
- 6 Curtiss (Winthrop) may be used as a salt substitute and saccharine in place of sugar. Baking soda (sodium bicarbonate) must not be employed in cooking.

Where indicated, digestive aids such as dilute hydrochloric acid, bile salts and pancreatic enzymes should be administered.

3 EPILEPSY

It is generally agreed that convulsive seizures or epilepsy like migraine does not represent an etiologically distinct disease entity. In a relatively small percentage of cases, an underlying allergy seems to play a dominant or at least a considerable rôle.

Some authors have come to regard migraine as "sensory epilepsy." This view is based not only on certain clinical similarities but particularly on the fact that there are some families in which epilepsy appears to be hereditary and in which there is also a high incidence of migraine. Buchanan^{297a} for one described a family in which there were 44 cases of epilepsy and 20 of migraine. Ely^{297b} found that the ascendants of migraine patients show a 71 per cent incidence of migraine and a 5.7 per cent incidence of epilepsy. In a series compiled by Stieffer^{297c} 75 migraine patients were related to epileptics. Spangler^{297d} claimed to have ascertained that the parents and siblings of 100 epileptics had histories of migraine in 77 instances, asthma in 44, urticaria in 17, hay fever in 12 and dermatitis in 8 instances, and that the siblings of these 100 epileptics included 46 cases of clinical allergy. More recently, Spangler^{297e} reported a series of 205 patients with convulsive seizures of whom 171 had a positive family history and 100 personal histories of allergy. Fifty-four instances of allergy were noted among the brothers and sisters of the patients. Eosinophilic counts were as high as 26 per cent and often showed an increase following treatment by injections of crotalin and dilantin, such cases yielding the best therapeutic results from this treatment. Balyeat^{298a} observed the concomitant occurrence of epilepsy, migraine and asthma in one family. Riley,^{298b} on the other hand, found that migraine was much less

^{297a} BUCHANAN, J. A. *New York M. J.* 113: 45, 1921.

^{297b} ELY, T. A. *Arch. Neurol. & Psychiat.* 24: 943, 1930.

^{297c} STIEFFER, C. *Deutsche Zeitschr. f. Nervenh.* 81: 110, 1924.

^{297d} SPANGLER, R. H. *J. Lab. & Clin. Med.* 13: 41, 1927; *J. Allergy*

3: 39, 1931.

^{297e} IDPM. *Ann. Allergy* 1: 91, 1943.

^{298a} RILEY, H. A. *Bull. Neurol. Inst. New York* 2: 429, 1932.

frequently associated with epilepsy than with other allergic disorders.

In a study of 1,000 epileptics, Ward and Patterson²⁹¹ obtained positive skin reactions in 48 per cent. Among 100 epileptic psychotics, Beauchemin²⁹² found that 80 per cent reacted to skin tests with various meats, 64 per cent to cereals, and a few to vegetables, while a high percentage of reactions occurred when tests were made with various endocrine extracts such as adrenal, thyroid, parathyroid, thymus, ovarian, and testicular. This latter observation requires further study. Moreover, positive skin tests in themselves are of little significance if it cannot be shown that avoidance of the incriminated foods brings relief and that their ingestion causes new convulsive seizures (see below).

Far more important, however, than the question of heredity or skin reactions are a number of carefully observed and experimentally proved cases of allergic origin. In these the epileptiform attacks were shown to have been elicited by certain foods or other allergens, while avoidance of specific exposure (or other appropriate measures) prevented appearance of the convulsions. The first experimentally confirmed case seems to be that reported by Pagniez and Lieutaud²⁹³. These authors succeeded in evoking epileptiform attacks by feeding the patient chocolate, and forestalled an attack by having the patient take an infinitesimal amount of chocolate forty-five minutes before eating an appreciable quantity. Numerous other authors (Ward,²⁹¹ Howell,²⁹⁴ Wallis, Nicoll, and Craig,²⁹⁵ Rowe and Richet, Jr.,²⁹⁷ Wilmer and Miller,²⁹⁸ Forman,²⁹⁹ Balyeat,²⁴⁴ Winkelman and Moore,²⁹⁰ McCready and Ray,²⁹⁹ Ball²⁹⁹) have reported identical cases in which the attacks of epilepsy were provoked by

absorption of allergens from the alimentary tract, and relieved by dietary restrictions. Kennedy²⁹² reported the case of a 2-year-old child who suffered from severe headaches, general convulsions, and giant urticaria. The attacks were of recurrent nature, and trial diet revealed a hypersensitiveness to milk. Elimination of this food resulted in complete cessation of all these manifestations. Wechsler²⁹³ described a case of epilepsy in which the attacks ceased completely after the causative agent (egg) had been identified. Pardee²⁹⁴ succeeded in evoking three series of typical epileptic convulsions in a nurse by oral administration of chocolate. Other observations have been reported by Dattner²⁹³ (cauliflower in one case, a number of animal proteins in another), Levin,²⁹⁶ Dewar²⁹⁷ (cheese), Adelsberger and Munter¹⁰⁰ (legumes), and Kauders²⁹⁸ (eggs).

In a few isolated cases it has been possible to identify allergens other than foods. Thus, Rowe²⁹⁶ reported a child with severe epilepsy associated with asthma, appearing in the summer. Rowe was able to prove an underlying hypersensitiveness to pollen. Appropriate specific therapy resulted in disappearance of both the epilepsy and the asthma. The same author reported another case, that of an 11-year-old boy who suffered typical petit mal attacks. Allergy to horsehair was found. After the patient's horsehair mattress had been removed, there was a rapid and complete cure. Forman²⁹⁹ also observed cases of epilepsy in association with pollinosis, and relieved by an allergic regimen. Clarke²⁹² and Rowe²⁹⁷ reported cases of convulsive seizures due to inhalants (animal emanations, pollens) along with foods. According to van Leeuwen, epileptic attacks can also be evoked by drugs.

Clarke²⁹² states that infantile convulsions are not infrequently due to allergic reactions of the central nervous system.

It must be borne in mind that in epilepsy, as in migraine and in numerous other condi-

²⁹¹ WARD, F. and PATTERSON, H. *Arch Neurol & Psychiat*, 17, 427, 1927.

²⁹² BEACHEMIN, J. A. *Am J Psychiat* 92, 1191, 1936.

²⁹³ PAGNIEZ, P., and LIEUTAUD, P. *Presse med* 27, 693, 1919.

²⁹⁴ WARD, F. *New York M J & Rec* 115, 592, 1922.

²⁹⁵ HOWELL, L. *Ohio State M J* 19, 660, 1923.

²⁹⁶ WALLIS, R. L. N., NICOLL, W. D., and CRAIG, M. *Lancet* 1, 741, 1923.

²⁹⁷ ROWE, A. H., and RICHEL, C., Jr. *J med franc* 19, 150, 1930.

²⁹⁸ WILMER, H. B., and MILLER, M. M. *J Allergy* 5, 628, 1934.

²⁹⁹ FORMAN, J. *Arch Neurol & Psychiat* 32, 517, 1934.

²⁹⁰ MCCREADY, E. B., and RAY, H. M. *M J & Rec* 120 (suppl) 117, 1924.

²⁹¹ BALL, F. E. *Am J M Sci* 173: 781, 1927.

²⁹² KENNEDY, F. *Arch Neurol & Psychiat* 15, 28, 1926.

²⁹³ WECHSLER, I. S. *J Nerv & Ment Dis* 88, 102, 1938.

²⁹⁴ PARDEE, D. *Arch Neurol & Psychiat* 39, 1360, 1938.

²⁹⁵ DATTNER, B. *Ztschr f d ges Neurol u Psychiat* 111: 632, 1927.

²⁹⁶ LEVIN, S. J. *J A M A* 97, 1624, 1931.

²⁹⁷ DEWAR, O. C. *J Ment Sci* 87, 608, 1941.

²⁹⁸ KAUDERS, F. *Wien klin Wchnsch* 48: 109, 1935.

²⁹⁹ ROWE, A. H. *J Nerv & Ment Dis* 99, 834, 1944.

tions that are at least occasionally due to allergy, the results of skin tests are by no means conclusive. They may serve as starting points for further search for the causative allergen but they must always be confirmed or disproved by the outcome of elimination and re-exposure tests.

In cases in which an allergen cannot be definitely demonstrated but in which an underlying food allergy is nevertheless strongly suspected, both Dattner²⁶⁶ and Singer²⁶⁷ recommend search for the allergen by means of the propeptan diet (see p. 190). Other authors advise treatment with peptone or tuberculin injections. Still others recommend a ketogenic diet, glutamic acid to acidify the urine, and of course, anticonvulsants.

4 OTHER CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Patients suffering from recurrent angioneurotic edema not infrequently present certain cerebral manifestations appearing either currently or alternately with those of the skin or subcutaneous tissues. According to Quincke²⁷⁹⁴ these conditions are due to edema of the pia encroaching upon the cortex. Osler²⁸⁰⁰, Quincke²⁷⁹⁴, Ohara,²⁸⁰¹ and van Bogaert²⁸⁰² reported the appearance of transitory paralysis of the oculomotor nerve, hemianopsia, optic neuritis, retrobulbar neuritis, evanescent aphasia, hemiplegia, convulsive seizures and partial unconsciousness. Rare cases include intermittent amblyopia due to allergy to garlic (Rowe and Richet²⁸⁰³) and amaurosis relieved by avoiding milk, corn and banana (Rowe and Richet²⁸⁰³).

Occasionally the cerebral symptoms in patients with angioneurotic edema are suggestive of those seen in serous meningitis (Vaughan and Hawke²⁴³⁷). However, similar meningo-cerebral manifestations have also been observed in the course of serum sickness (3 cases of Mason²⁸⁰⁴) and in hypersensitivity to milk (Kennedy²⁸⁰⁵) without angioneurotic edema. Ratner²⁸⁰⁶ recognizes three types of menin-

gitis resulting from serum injections: serum sickness meningitis due to extrathecal injection of serum and complicating an ordinary generalized serum sickness; aseptic or serum meningitis which results from the primary contact of the serum with the meninges after intrathecal injection and which is not an allergic response; and allergic meningitis following intrathecal injection after previous sensitization and fulfilling the criteria of an allergic reaction. The last type can even be elicited by an intravenous injection provided local sensitization of the meninges has been previously established.

Paralysis of cerebral origin simulating vascular lesions may be due to angioneurotic edema of the brain caused by injection of foreign serums as well as by internal absorption of allergens. Cases of hemiplegia following serotherapy have been reported by Morichau Beauchant and Fagart²⁸⁰⁶, Lerond²⁸⁰⁷, Kennedy²⁸⁰⁸, Bassoe,²⁸⁰⁹ Paillass²⁸¹⁰ and others.

The paralyzes are not always of short duration. Thus Winkelman and Moore²⁸¹¹ reported the case of a young man who complained of weakness of the right side of the body coming on slowly during a period of seven days. The condition was found to be attributable to hypersensitivity to seafood. Paralyzes due to food allergy were described by many authors. One of the writer's own cases—with numbness of both extremities of the left side due to hypersensitivity to pork—may be regarded as of cerebral allergic origin. In general, however, opinions differ as to whether the lesion in these cases is an urticarial edema of the cerebrum or of the sheaths of the peripheral nerves. Examples will be presented in the following section.

Encephalomyelitis following the use of serum was reported by Winkelman and Gotten,²⁸¹² meningocerebral manifestations attributable to hypersensitivity to milk by Kennedy²⁸⁰⁵. Ferraro²⁸¹³ believed that the brain changes which he observed in two cases

²⁶⁶ DATTNER, B. *Nervenarzt* 4: 3, 1931.

²⁶⁷ SINGER, A. *Wien. med. Wchnschr.* 87: 1070, 1937.

²⁸⁰⁰ OSLER, W. *Am. J. M. Sc.* 9: 362, 1885.

²⁸⁰¹ OHARA, L. *Van. Re. d. otol.* 12: 371, 1931.

²⁸⁰² MASON, V. R. *J. A. M. A.* 78: 88, 1912.

²⁸⁰³ RATNER, B. *Allergy, Anaphylaxis and Immunotherapy*.

Baltimore: Williams & Wilkins, 1943.

²⁸⁰⁶ MORICHAU BEAUCHANT, R. and FAGART. *Bull. et mem. Soc. med. d. hop. d. Paris* 45: 1406, 1921.

²⁸⁰⁷ LEROND, J. *ibid.* 50: 169, 1926.

²⁸⁰⁸ KENNEDY, F. *J. Ner. & Ment. Dis.* 88: 91, 1938.

²⁸⁰⁹ BASSOE, P. *M. Clin. North America* 16: 409, 1932.

²⁸¹⁰ PAILLASS, J. E. *Marseille med.* 1: 48, 97, 1936.

²⁸¹¹ WINKELMAN, G. W. and GOTTEN, N. *Am. J. Syph. & Neurol.* 17: 411, 1935.

²⁸¹² FERRARO, A. *J. Neuropath. & Exp. Neurol.* 3: 427, 1944.

of post-scarlatinal encephalitis were allergic in nature.

Acute cerebral edema as a local allergic phenomenon was reported by Espejo and Voto-Bernales^{17,23} in three cases following the third injection of neocarsphenamine. The prodromal symptoms included headache, vomiting, epigastric pain, diarrhea, and insomnia, while the acute manifestations were apoplectic, convulsive, or pseudoepileptic. Both Rowe²⁹⁹ and Crowe³⁰³ described instances of cerebral edema due to foods and controlled by elimination diets.

Ferraro³⁰⁴ introduced the concept that demyelinating diseases, especially of the acute form, are the expression of a cerebral allergic reaction. He based his contention on the fact that in these conditions one finds the fundamental histologic features of cerebral allergy. This viewpoint, in his opinion, opens new avenues to the interpretation of the pathogenesis and histogenesis of multiple sclerosis, diffuse sclerosis, and the acute encephalomyelitides. Hurst³⁰⁵ reviewed the question of allergy and demyelination and expressed the opinion, based on original animal experiments, that at the moment final conclusions do not appear to be warranted.

A case of periarthritis nodosa of the cerebral vessels with decerebrate rigidity and extensive encephalomalacia in a 5-year-old child was described by Malamud.³⁰⁶ At necropsy, massive necrosis of the cerebrum was found. Microscopic examination revealed typical changes of periarthritis nodosa in the smaller meningeal arteries, with similar lesions in the heart and other organs. Since periarthritis nodosa is now considered as due to an allergic reaction of blood vessel walls, Malamud assumed that the clinical symptoms and pathologic lesions present were a general allergic reaction of the brain tissue.

There is sometimes a multiplicity of nervous symptoms in allergic states that cannot possibly all be accounted for on the basis of a single lesion. Thus, Winkelman and Moore²⁹⁰ reported a case in which the manifestations included diplopia, weakness of the right side of the face, ringing in the ears, vertigo, stag-

gering gait, and attacks of yawning. The patient remained free of symptoms as long as he abstained from seafood.

Finally, a number of inexplicable nervous manifestations—including irritability, mental obtundity, and isolated cases of various forms of psychic disturbance—may perhaps be of cerebral-allergic origin. However, it must be stressed once again that this diagnosis is not to be made without confirmation by the results of appropriate elimination and re-exposure tests. In this category are, for example, a case of insomnia attributable to oranges and blackberries (Rowe and Richet²⁸⁷), insomnia due to milk and in other instances to chocolate or cauliflower (Adelsberger and Munter¹⁰⁸), cases of hypersomnia and one of narcolepsy (Urbach and Wilder³⁰⁷); seasonal somnolence due to ragweed pollen, unaccompanied by symptoms of hay fever or asthma (Sternberg¹⁹⁰), recurrent attacks of mental confusion caused by dog and cattle hair (Clarke²⁹²); and in addition, certain cases of uncontrollable yawning observed by the authors (it is to be noted that the last-named symptom is also a frequently observed prodromal sign of anaphylactic shock). Moreover, according to Dattner,³⁰⁰ many cases of anxiety and compulsive states and of mental depression are due to hypersensitiveness to foods. Vaughan³⁰⁸ holds that this may be the cause of many otherwise inexplicable manifestations of fatigue, particularly in children. He cites the case of a young woman who was always unspeakably tired so long as she ate dishes made from wheat flour, but who became a very energetic person when she excluded this food from her diet. Practically identical observations were made by the present writers. Cases of otherwise intractable fatigue have been seen to vanish when the nutritive allergen was eliminated from the diet or when propeptan was administered.

According to Clarke²⁹² numerous cases of high-strung, nervous, unruly, disagreeable, and even incorrigible children, who showed none of the accepted manifestations of allergy, have been found to be hypersensitive to foods—most commonly wheat. Proper therapy changes their attitude toward life and restores

³⁰³ CROWE, W. R. *J. Allergy* 13: 473, 1942.

³⁰⁴ FERRARO, A. *Arch. Neurol. & Psychiat.* 52: 443, 1944.

³⁰⁵ HURST, E. W. *Brain* 67: 103, 1944.

³⁰⁶ MALAMUD, N. *J. Neuropath. & Exper. Neurol.* 4, 88, 1945

³⁰⁷ URBACH, E., and WILDER, J. *Med. Klin.* 38: 1420, 1934.

³⁰⁸ VAUGHAN, W. T. *Virginia M. J.* 56: 735, 1930.

a normal personality. Alvarez and Hinshaw¹⁰⁰ state that food can at times produce mental depression, drowsiness and a number of curious sensations in the head. It has been repeatedly suggested that cyclic vomiting in children is due to a cerebral reaction rather than gastro intestinal allergy and may be a sort of precursor of adult migraine. Kennedy and Williams¹⁰¹ have even advanced the hypothesis that stammering is often a symptom of allergy. But Forman¹⁰² disagrees holding that it may merely be due to the nervous strain under which the allergic child suffers.

Rowe¹⁰³ has employed the term allergic toxemia to designate symptoms characterized by fatigue, mental confusion, drowsiness, inability to concentrate, irritability, generalized body aching and chilliness occurring in various combinations and degrees. He holds that meningeal and especially cerebral edema and possibly vascular spasm with reactions in other body tissues are probably responsible. It is due chiefly to food but also to pollen allergy. Other allergic manifestations are usually present. Among the psychoneurotic disturbances due to cerebral allergy he lists restlessness, incorrigibility, bursts of temper, phobias, drowsiness, nightmares, inattentiveness and restlessness during sleep. These usually occur in children. Randolph¹⁰⁴ observed a series of cases of fatigue and weakness unrelieved by an adequate or even excessive amount of rest and chiefly due to uncontrolled food sensitivity. Other nervous symptoms such as mental sluggishness, vagaries of memory, irritability, crankiness and various degrees of emotional depression were frequent concomitants. Some patients exhibited abnormalities of the blood cells (Randolph and Gibson¹⁰⁵) but complete examination was usually negative. Although the condition resembles a psychoneurotic disturbance it may be recognized by the high incidence of other allergic disorders or of a past history of allergic disease and the results of elimination diets and careful feeding tests. Any age group may be affected.

Ferraro¹⁰⁶ suggested the possibility that allergic reactions may be the basis for some acute mental upsets through allergic shocks originated by autogenous mechanisms in which the brain might represent the shock organ. Because such a pathologic state is reversible in its mild and initial stages (edema, swelling, perivascular reaction) its appearance and disappearance may be reconciled with the onset and clinical remission of acute mental episodes. The field of allergy in both its clinical and pathologic implications may thus constitute a new and fertile realm of investigation in psychiatry.

Zelzer¹⁰⁷ studied the electroencephalograms of a group of patients with hay fever, asthma, urticaria and rhinopathy. Alterations of the wave components consisting of abnormally fast or slow records were found in 39 per cent of these cases in comparison with 20 per cent of normal subjects. While the altered brain waves are not diagnostic of allergy they occur with a higher incidence in allergic persons than in nonallergic. In the cases of hay fever electroencephalograms were made before, during and after the hay fever season but the only change noted was that during the season the waves indicated increased muscle activity due to increased muscle tension as a separate entity superimposed on the brain wave.

C. PERIPHERAL NERVOUS SYSTEM

Neuritic or neuralgiform manifestations even when appearing during the course of or as sequelae to allergic diseases are to be regarded as of allergic origin only when they subside on elimination of the antigens and reappear after re-exposure to them.

Thus Mathieu¹⁰⁸ reported the case of a man who developed respiratory difficulty, unconsciousness and a right brachial plexus palsy after ingestion of crabmeat. Funck described a case in which ingestion of 65 Gm of Camembert cheese elicited among other allergic symptoms an attack of lumbago that was so painful that it caused the patient to faint. In a patient reacting to pork with urticaria the present writers found that both the cutaneous and neuritic manifestations could be deliberately evoked by ingestion of

¹⁰⁰KENNEDY A. M. and WILLIAMS D. V. B. 1. M. J. 2. 1936
1938

¹⁰¹FORMAN J. Ohio State M. J. 35. 1. 1939

¹⁰²RA. DOLPH T. G. Ann. A. C. 7. 3. 4. 194

¹⁰⁶FERRARO A. Psychiat. Quart. 19. 6. 194

¹⁰⁷ZELEZER E. Laomed. du Canada 61. 3. 19

this food, and could be inhibited by administration of specific propeptans. Neuritides in the regions of the upper and lower extremities are sometimes observed in hay fever (those appearing only after therapeutic pollen injections are naturally not included here). Kennedy and others have reported that they may also sometimes be associated with asthma, migraine, or urticaria. A case of facial neuralgia due to house dust was described by Craft¹⁸⁷. Rowe²⁹⁹ pointed out that neuralgia, aching distress, and less often paresthesias due to food allergy may take the form of low back or sciatic pain, and may even simulate sacro-iliac and lower lumbar arthritis. "Algiae allergicae" is the designation given by Moreno²⁹² to painful conditions caused by an allergic mechanism. In his opinion, certain cases of intercostal neuralgia, sciatica, and arthralgia may be of allergic origin.

Furthermore, there are some quite exceptional cases in which neuritides or neuralgiform pains are the only expression of a hypersensitiveness; however, this possibility is to be accepted only when the patient reveals a tendency to other allergic reactions. Thus, Dattner³⁰⁰ described paresthesias in the arms and legs following ingestion of large quantities of oranges and lemons. Adelsberger and Munter¹⁰³ reported a case of allergic neuritis due to eating asparagus, another case due to coffee, and a third, to milk. Rowe and Richet²⁹⁷ observed a case of brachial neuralgia attributable to hypersensitiveness to wheat. Ross³⁰⁴ cited a case of peripheral neuritis due to hypersensitiveness to allergens in the honey bee.

Mention must also be made here of a third group of neuritides appearing during or after serum therapy. These commonly affect branches of the cervical and the brachial plexus (Kraus and Chaney,³⁰² Robinson,³⁰⁶ Doyle,¹²⁹ Wilson and Hadden²⁹⁷), although cases involving the recurrent laryngeal and auditory nerves have been described. Clarke²⁹² states that more than 100 cases have been reported. The majority of authors

explain these neuritides as attributable to an edema in or around the nerve tissue, resulting in an ischemic paralysis of the nerve trunks or peripheral nerves, others, however, attribute them to the toxic substances formed in the course of the serum therapy; still others believe that they are due to pressure on the nerve in the intervertebral canal, resulting from either an edema of the sheath at that point or from an urticaria of the spinal meninges. As already mentioned, an urticarial lesion of the cerebrum can also produce paralysis due to allergy. Neuritides are almost always preceded by and at times may be the only clinical manifestation of serum sickness. These neurologic complications are usually transitory but may occasionally persist for from six to twenty-four months. According to Bennett, a permanent residual weakness remains in about one-fifth of the cases.

Moreover, paralyses of the brachial plexus, and less often of the peroneal group, have frequently been encountered. Schipkowensky¹²⁹ has collected 80 cases of this sort from the literature. He believes, however, that these conditions are more common than this figure would indicate.

In this connection, it must be mentioned that myalgias may also occasionally be produced allergically.

Pruritus may be the first and even the only expression of an allergic reaction. Generalized pruritus is notoriously a common forerunner of urticaria, lichen urticatus, or dermatitis. Strictly localized pruritus ani can likewise be caused allergically. Thus, Tuft¹¹² described the case of a physician who had marked itching and pain in the rectum after each ingestion of egg. Other examples of allergic pruritus ani are cited on page 678. Schapiro and Albert²⁵⁰ found in 15 per cent of their cases of pruritus ani that elimination of the allergens eliciting positive intradermal reactions resulted in improvement.

Some evidence has been presented showing that the severe local tissue reaction in highly sensitized experimental animals or in man is due in part to degeneration of nerve fibers in the area. Thus, Lasowsky and Kogan²⁰²

¹²⁹ MORENO, J. *Prensa med argent* 23: 1567, 1936.

¹⁸⁷ ROSS, A. T. *J. Allergy* 10: 382, 1939.

³⁰² KRAUS, W. M., and CHANEY, L. B. *Arch. Neurol. & Psychiat* 37: 1035, 1937.

²⁹⁷ WILSON, L. J. *New England J. Med.* 216: 531, 1937.

²⁹⁹ WILSON, G., and HADDEN, S. B. *J.A.M.A.* 98: 123, 1932.

²⁰² LASOWSKY, J. M., and KOGAN, M. M. *Virchows Arch. f. path. Anat.* 292: 428, 1931.

demonstrated that in normergic animals the damage to the individual nerve fibers can be observed only at the peak of the inflammation (usually forty eight hours after the beginning of the reaction), in hyperergic inflammations, on the other hand, as in the Arthus phenome-

non, the involvement of the nervous system is both more prompt and far more severe. Within three hours after the serum is injected into the muscle tissue of a sensitized rabbit, a great many degenerated nerve fibers can be seen.

CHAPTER XXVII

ALLERGIC DISEASES OF THE EYE

ALLERGIC eye manifestations can be of various origins. They may be due to (1) the local action of an exogenous allergen, (2) generalized hypersensitiveness, the allergen reaching the eye by way of the blood or the lymph stream; (3) focal reactions of bacterial-allergic origin; and (4) focal reactions attributable to an underlying metallergic state. The precise disease picture produced depends largely on which ocular tissue is the shock structure.

It is also possible that certain ocular diseases may be explained on the basis of the Schwartzman phenomenon—local tissue reactivity to bacterial filtrates (see p. 31). Schwartzman³⁰²³ suggests that the vulnerable state may be produced, possibly during the course of some insignificant or even unrecognized infection, by bacterial toxins or by localized bacterial or virus infections. The provocative factor may be bacterial toxins, nonbacterial antigen-antibody complexes, or live bacteria carrying the toxins, and may be effective only when reaching the vulnerable tissue by way of the general circulation.

Any portion of the eyeball or of its coverings may be involved in an allergic reaction. While in many cases only one particular tissue (e.g., conjunctiva or cornea) is affected, others may show involvement of several or even all parts of the eye, either simultaneously or successively. However, for purely didactic reasons, the allergic manifestations in the various structures of the eye will be discussed separately.

A. EYELIDS

While the lids do not, strictly speaking, belong to the structures of the eye proper, mention of the allergic diseases of the eyelids will be included here for the sake of completeness. The lids may be affected alone or along with other skin areas, or, although quite rarely, together with one or more parts of the eyeball.

The most common of all the allergic dermatoses of the lids is contact dermatitis. The

acute form is characterized by an erythematous swelling, usually of the upper lids, occasionally, the lower lids are also involved. If the offending agent is not identified and removed, the disease may become chronic.



FIG. 393 ALLERGIC CONTACT DERMATITIS AND CONJUNCTIVITIS DUE TO INSTILLATION OF ATROPINE EYE DROPS

Reaction to patch test with 0.1 per cent atropine was so severe that it had to be removed after four hours.

It is then characterized by a brownish, parchment-like, wrinkled, scaling appearance, often accompanied by itching. The eliciting allergen is usually found to be a drug used in the eyes, such as atropine (FIG. 393), local anesthetics, or yellow oxide of mercury, or nail polish, cosmetics, perfumes, and not rarely poison ivy. The condition may, however, be due to a food allergen, such as egg, coming into contact with the eyelid by way of the fingers (FIG. 394). In a series of 36 cases of dermatitis confined to the eyelids, Hazen¹⁴³¹

³⁰²³ SCHWARTZMAN, G. J. *Mc. Surg. Hosp.* 11: 21, 1944

found the following offenders nail lacquer orange peel carbon paper wave set lotion hair dye face powder dog hair coll cream sulfur ointment ammoniated mercury and soap powder Because of differences in the thickness and vascularity of the skin patch tests performed elsewhere with the responsible contactant may be negative

Angioneurotic edema may be confined to the eyelids or appear there as part of a general reaction It quite frequently occurs in serum sickness but may be due to food or drug

predispose to their development Moreover some authorities have speculated that an allergic state may directly underlie the process Ruedemann³⁰¹ attributed a case of recurring styes to the eating of chocolate

Lastly Loevenstein in the last of his experimental work and of histologic investigations advanced the theory that chalazions are caused by repeated resorption of the secretion of obstructed meibomian glands Such resorbed material may act as an endogenous allergen the chalazion constituting the

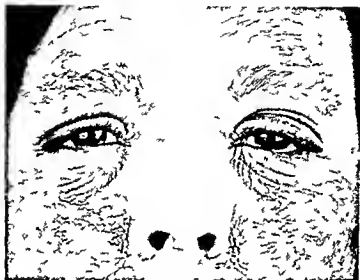


FIG 394 ERYTHEMA AND EDEMA OF PLELIDS IN CASE OF NEURODERMATITIS

Symptoms were produced by accidental contact with raw egg white during cooking and by deliberate experiment

hypersensitiveness and to numerous other causes

In occasional instances blepharitis may be of allergic origin It is frequently associated with chronic palpebral conjunctivitis and sometimes with dermatitis involving the scalp the areas behind the ears and the nares Bab³² was able to identify dust feathers and horse hair as allergens in this condition Berneaud³⁰³ ointments and Bothman³⁰⁷ cow's milk

Although hordeoli or styes are suppurative lesions such conditions as blepharitis dermatitis and conjunctivitis of allergic origin may

local allergic response In one case of recurring chalazions of all the lids associated with marginal blepharitis and chronic conjunctivitis Bothman³⁰⁷ succeeded in achieving a lasting cure of all the symptoms by limiting but not entirely eliminating the intake of meat

B CONJUNCTIVITIS

Allergic conjunctivitis may be divided into three types (Lagrange and Delth³⁰⁵)

The first is the acute edematous form characterized by a sudden onset and by edema of the bulbar and even of the palpebral conjunctiva with injection of the conjunctival vessels itching and lachrimation This condition is

³⁰⁰ B B W A h f Ophth 328 238 1932

³⁰¹ BERNEAUD G Zi h f Augenh 8 193 1932

³⁰² B THMAN L The 1941 Year Book of the Eye Ear Nose and Throat Chicago Y Bk Pub 1941 p 7

³⁰³ RUEDEMANN A D Ohio State M J 30 304 1934

³⁰⁴ LAGRANGE H and DELTH L S Ann d ocl 1 8 1009 1933

usually caused by air-borne allergens. It is often but not necessarily seen in association with other allergic manifestations, particularly hay fever, as well as rhinopathy and asthma of exogenous origin. The secretion is slightly mucoid and on examination of the stained smear shows a predominance of eosinophils. The mucous membrane involvement sometimes accompanies angioneurotic edema of the eyelids. Besides pollen, the chief offenders are air-borne fungus spores, principally *Alternaria* and *Cladosporium* (Simon¹⁰¹⁶), and also house dust (Lehrfeld,³⁰²⁵ Cohen³⁰²⁶). In occasional instances, feathers, horse dander, animal hair, and animal blood have been found to be the causes.

Manger, for one, reported a typical case of this kind. A pharmacologist who always had attacks of asthma and rhinopathy after bloody operations on cats (but not from handling uninjured ones) once accidentally got a drop of cat's blood in his eye; after a few seconds, there were marked swelling of the conjunctivae, injection of the vessels, and edema of the eyelids, as well as intense pruritus and photophobia.

However, the allergen can also reach the conjunctival mucosa by way of the blood stream, chiefly from the gastro-intestinal tract. The following have been proved to be causal agents transported by this route: wheat and milk (Rowe⁷⁴⁹), apricot preserves (Strebel), fish (Frausnitz and Kuestner⁴²³), horse meat (Nicolau), iodides or salicylates (van der Hoeve). For additional references, see Bothman.³⁰²²

The various sulfonamide compounds, orally administered, are particularly prone to produce this type of reaction. The conjunctivitis may accompany any of a variety of allergic responses, or may be an isolated finding.

These conjunctivides are occasionally the vicarious expression of or actually the equivalent of some other allergic disease, such as asthma (Vallery-Radot et al.³⁰²⁷)

Conjunctivitis due to hypersensitiveness need not necessarily be allergic in character; some occasional cases are attributable to an

underlying pathergic state. As an example, one might cite the changes in the bulbar conjunctiva observed by Bezecky and Bieringer in a case of summer prurigo (light hypersensitiveness due to porphyrin). Furthermore, certain conjunctivides due to bacterial toxins might be regarded as Schwartzman phenomena in the eye (Sanders³⁰²⁸).

The second type is the so-called eczematous conjunctivitis. It is characterized by dermatitis and swelling of the lids and often of the adjacent skin, as well as by profuse lacrimation, conjunctival congestion, and slight chemosis. It is caused chiefly by the drugs commonly used in the treatment of eye diseases, such as atropine and its derivatives, cocaine and its substitutes, including procaine and butyn, dioun, eserine, pilocarpine, zinc sulfate, yellow oxide of mercury, scarlet red ointment, and even petrolatum. This form of the condition is very often accompanied by marked epidermal hypersensitiveness, as shown by positive patch tests with the offending substances. In addition, other kinds of exogenous allergens may also be the causes in occasional instances: henna in eyelash dyes (Bab³⁰²⁹), orris root (Eggston³⁰³⁰), flowers such as asters, dahlias, chrysanthemums (Strebel), primroses (Bufe), and even cocobolo wood (Meister), as in a patient who played a flute made from this material. In such cases, it is often difficult to establish the etiology in the absence of other allergic manifestations.

The third type is a chronic recurrent conjunctivitis, often associated with redness of the free borders of the lids and folliculosis of the palpebral conjunctiva, giving rise to a velvety, boggy appearance, as well as with a stringy mucoid secretion. It is characteristic that bacteriologic investigation does not reveal any infection. Pollens (Lemoue²⁷⁴⁰), feathers or foods (Balyeat and Bowen³⁰⁴¹), and silk (Taub³⁰⁴²) are often found to be the allergens. Linhart³⁰⁴³ found that in about one-third of his cases of chronic recurrent allergic conjunctivitis, corneal involvement could be

³⁰²⁵ LEHRFELD, L. Arch Ophth 8: 369, 1932

³⁰²⁶ COHEN, A. E. J. Allergy 13: 170, 1942

³⁰²⁷ VALLERY-RADOT, L. P., BLAMONTIER, P., and STREBELIN, J.: Presse méd. 37: 529, 1929.

³⁰²⁸ SANDERS, T. E. Am J Ophth 22: 1071, 1939

³⁰²⁹ EGGSTON, A. A. Laryngoscope 32: 817, 1927

³⁰³⁰ LEMOINE, A. Tr. Am. Acad. Ophth 1925, p. 198

³⁰⁴¹ BALYEAT, R. M., and BOWEN, R. South M J 28: 1005, 1935

³⁰⁴² TAUB, S. I. J. Allergy 7: 75, 1936

³⁰⁴³ LINHART, W. O.: Arch Ophth 31: 403, 1944

demonstrated by slit lamp examination, although not detected on gross examination

Aside from the eczematous type, skin testing should be performed by the scratch or intradermal methods, if the suspected allergen is such as to make such tests feasible. However, it is important to note that in some instances of allergic conjunctivitis (or, more properly, allergic conjunctivopathy), skin tests may be completely negative (Berneaud³⁰³³). Moreover, ophthalmic tests should be undertaken only with the greatest of caution and with high dilutions in view of the danger of severe reactions. It is a feature of ocular manifestations, sometimes called conjunctival crises, that the violent subjective complaints are often in striking contrast to the slight objective findings and also that the symptoms tend to recur and become exacerbated. The presence of an underlying allergy is strongly suggested when the secretions in the conjunctival sac are found to contain many eosinophile cells.

C VERNAL CONJUNCTIVITIS

While vernal catarrh is likewise a form of conjunctivitis, it will be discussed separately here because of its distinctive clinical appearance and pathogenetic background. Duke Elder³⁰⁴⁴ gives the following comprehensive definition of this disease: "Vernal conjunctivitis is a recurrent bilateral, interstitial inflammation of the conjunctiva, of seasonal incidence and (as yet) unknown etiology, characterized by flat topped papules, usually on the tarsal conjunctiva, resembling cobblestones in appearance, a gelatinous hypertrophy of the limbal conjunctiva, either discrete or confluent, accompanied by corneal involvement, and associated with itching, redness of the eyes, lacrimation, and a mucinous or lardaceous discharge usually containing eosinophils." It is more common in children than in adults.

There are two types of this disease, namely, the limbic and the lid form. The former is usually localized on the bulbar conjunctiva near the limbus, appearing as vesicles which may coalesce to form gray crescentic or annular lesions. Histologically, this limbic type may be compared with a wheal as seen in allergic reactions of the skin (Bothman³⁰³²).

The palpebral type is subdivided into the simple follicular, the pavement epithelium (cobble stone), and the granuloma or giant cobblestone form. Pathologic specimens of the conjunctiva show, among other changes round cell infiltration, hyperplasia of the fibrous tissue, and eosinophils. Because of the increased activity of the disease during the warm seasons, it is often referred to as spring catarrh or vernal catarrh.

The many theories concerning the etiology of vernal conjunctivitis have been ably covered in a recent review of the subject by Eber³⁰⁴⁵. We are here concerned only with those views that attempt to show that the condition is based on a specific conjunctival hypersensitivity to certain antigens. The protagonists of these theories are Lehrfeld,^{3046, 3048} Lagrange and Delteil,³⁰⁴⁴ and Woods³⁰⁴⁷. The allergic theory is supported by (1) the clinical recurrences and the associated itching, (2) the climatic, geographic, and seasonal incidence, (3) the frequent association of vernal conjunctivitis with other allergic manifestations such as asthma, hay fever, urticaria, angioneurotic edema, and neurodermatitis, (4) the reaction of the conjunctiva, in patients so afflicted, to specific allergens, (5) the fact that subjective symptoms are relieved by the instillation of epinephrine into the eyes, and (6) the absence of bacteria and inclusion bodies, as well as the presence of eosinophils in the conjunctival secretions. Tuft¹⁴² ventures the opinion that vernal conjunctivitis belongs to the contact types of allergy produced by sensitivity to fat-soluble excitants, this concept is well supported by Bowen's³⁰⁴⁸ findings that treatment with the oily fraction of pollen is often very helpful, while the water soluble fraction is of no value. However, Albert and Walzer¹⁴⁷ employed oil-free extracts of the common allergens in petrolatum for patch testing—preparations not ordinarily used for this purpose—and elicited contact reactions in some cases of vernal catarrh that gave negative responses to intracutaneous tests with the same allergens. Although a high percentage of reactions to silk-worm and feathers was obtained with this method in children with vernal conjunctivitis,

³⁰⁴⁴ DUKE ELDER C T J Missouri M J 39 171 1942

³⁰⁴⁵ LEHRFELD L Am J Ophth 8 368 1925

³⁰⁴⁶ WOODS A C Arch Ophth 17 1 1937

³⁰⁴⁷ BOWEN R South M J 34 134 1941

these authors were unable to demonstrate an etiologic relationship. Further studies are being pursued with this technic. In any case, the majority of investigators are of the opinion that certain predisposing factors—particularly endocrine disturbances and imbalance of the autonomic nervous system—are necessary to pave the way for sensitization of the conjunctivae.

There is some disagreement as to the nature of the allergens most commonly involved. Lehrfeld and Miller,³⁰⁹ using the intradermal method of testing, found dust, feathers, silk, tobacco, wool, goat epithelium, orris root, kapok, and pollen to be the substances most frequently eliciting positive reactions. In addition, many patients responded clinically to ophthalmic tests with the dry pollens of grasses. In Bowen's³⁰⁴ series, likewise, 40 per cent of the patients were found to be sensitive to pollens. Marton³¹⁰ described four cases of severe vernal conjunctivitis with negative or only faintly positive scratch and intracutaneous tests to pollen. However, since the onset of the condition corresponded to the pollination seasons, they were given intensive treatment with the appropriate pollen extracts, rapidly reaching a dose of 1 to 2 cc. of a 1:50 dilution. Excellent therapeutic results were achieved.

The senior author observed a 5 year old boy who gave negative cutaneous and intracutaneous tests. However, conjunctival tests with ragweed were maximally positive. Ragweed hyposensitization by the subcutaneous route prevented the occurrence of the vernal catarrh despite the fact that the child had had it for three consecutive years. Other authors, led by Cooke,³¹¹ discount the theory of pollen etiology. Cooke, however, developed the concept that vernal catarrh is an allergic condition analogous to hyperplastic sinusitis—i.e., a bacterial allergy. He based his views on the satisfactory clinical improvement following the removal of infected foci such as tonsils and teeth, and on the response to treatment with autogenous vaccines. On the basis of skin and conjunctival tests, Feinberg³¹² suspects that the disease is due to hypersensitiveness to fungus spores. Intracutaneous tests gave rise

to delayed-type reactions. Lastly, the theory was advanced that vernal conjunctivitis is attributable to hypersensitiveness to light based on a sensitizing substance, such as porphyrin, present in the organism (Junius, Meves).

The treatment is generally symptomatic. Lehrfeld suggests, among other local anesthetics and astringents, the use of phenacaine, 3 drops of a 1 per cent solution as frequently as necessary, followed immediately by 3 drops of 1:1,000 epinephrine. For removal of the mucoid discharge from the conjunctiva, flushing with a cold saturated solution of boric acid is recommended. If the pathologic changes in the tarsal conjunctiva have reached an advanced stage or if a corneal ulcer is present, it is advisable to resort to the aid of an ophthalmologist for topical or surgical treatment.

In cases in which specific positive reactions are elicited by means of skin or preferably ophthalmic testing, the excitant should be eliminated, when this is impossible hyposensitization should be tried. As mentioned above, Bowen³⁰⁴ reported good results with the oily fraction of pollen, while extracts containing only the aqueous principle were found unsatisfactory. However, patch tests with the fat-soluble excitants were invariably negative. Furthermore, Cohen³⁰⁶ obtained good results with injections of house dust extract in a case in which instillation of a drop of the dilute extract in the eye called forth a marked ocular reaction, although the scratch test was completely negative.

D. PHLYCTENULAR KERATO-CONJUNCTIVITIS

Ever since the basic experimental work of von Szily,³⁰² the view has been generally accepted that phlyctenules are the result of an allergic reaction taking place in the cornea and conjunctiva (Woods³²¹). It was formerly believed that this occurred only as a result of sensitization arising from a small early tuberculous focus in the eye, or as a part of a general hypersensitiveness to tuberculo-protein from lesions elsewhere in the body. However, Schieck observed phlyctenules in an eye infected with gonococci, in a patient with a

³⁰⁹ LEHRFELD, L., and MILLER, J. *Arch. Ophth.* 21: 639, 1939.

³¹⁰ MARTON, S. *Ann. Allergy* 1: 39, 1943.

³¹¹ COOKE, R. A. *J. Allergy* 8: 279, 1937.

³¹² SZILY, A. *von Klin. Monatsbl. f. Augenh.* 51: 164, 1913.

chronic gonococcal arthritis Bothman³⁰³² was able—by means of hyposensitization in 3 cases and by the results of elimination diets in 2 others—to demonstrate that pollens and foods respectively were the causal agents O'Brien and Allen³⁰³³ state that the etiologic agent in allergic keratoconjunctivitis may be determined by the history cutaneous or patch tests or the method of elimination A local eosinophilia may or may not be demonstrable in scrapings from the conjunctiva In 5 cases reported by them the offending allergens were orange (with positive patch test and recurrence after ingestion of orange) butyric hydroxy wool fat in an ophthalmic ointment a proprietary nasal inhalant and a fur coat, respectively Lehrfeld observed cases of allergic phlyctenular keratitis due to strawberries and face powder Riehm³⁰³⁴ confirmed the experimental work of Funaishi and Morelli showing that phlyctenules can be produced by instillation of the allergen in the conjunctival sacs of experimental animals previously injected with protein substances

Although the tuberculous character of phlyctenules in the overwhelming majority of cases has been definitely established, Moro and Keller¹²⁶ point out that the condition is of allergic origin in occasional instances They called attention to the fact that phlyctenules not infrequently develop simultaneously with the appearance of hypersensitiveness to tuberculin Furthermore, a metallergic mechanism may be involved Thus Rubert reported that he succeeded in inducing phlyctenules in tuberculous animals not only with tuberculin but also with staphylococcal toxin Guillery made the same observation in regard to human beings

E INTERSTITIAL KERATITIS

As first demonstrated by Wessely³⁰³⁵ a rabbit given a preliminary intracorneal injection of horse serum and a dose of 0.05 cc of the same antigen into the cornea twelve days later, will develop severe keratitis and iritis within twenty four hours According to von Szily,³⁰³⁶ the same reaction will invariably appear if the reinjection is made intravenously In man, interstitial keratitis has been traced

in occasional instances to allergic influences Mauksch³⁰³⁶ Anneberg³⁰³⁷ and Bitlman³⁰³² found hypersensitiveness to pollen to be the underlying cause in their material Woods³⁰³⁸ reported 2 cases found to be due to corn dust and relieved by hyposensitization with corn extract In a farmer Noe³⁰³⁹ observed four attacks of keratitis each directly associated with working with corn it was found that corn smut was the allergen and the patient was cured by hyposensitization with corn smut extract Bothman³⁰³² had a patient sensitive to molds and prevented further attacks by treatment with a specific extract The presence of food allergy was demonstrated by Dean and his associates³⁰⁴⁰ in 6 cases first by relieving the symptoms by means of withdrawal of certain foods from the diet and then by reproducing the clinical manifestations by deliberate feeding Lemoine³⁰⁴¹ similarly demonstrated the existence of food allergy in 2 instances

Parlato³⁰⁴² observed a nun with corneal ulcers caused by hypersensitiveness to the sachets used in church vestments the patient gave positive reactions toorris root Moran³⁰⁴³ and others reported the same condition in association with severe dermatitis of the face due to the application of hair dye to the eye brows and lashes

A particularly interesting question is whether interstitial keratitis in cases of congenital syphilis may have an allergic pathogenesis There are three different views Igersheimer¹⁷⁹⁷ postulates that the spirochetes present in the corneal tissue of the congenital syphilitic are resorbed and thus sensitize the corneal parenchyma This takes place without calling forth any manifest reaction But when new spirochetes coming from organs newly involved by the specific infection reach the hypersensitive corneal tissue by way of the blood stream they elicit an allergic reaction in the cornea Schieck¹⁷⁹⁸ on the other hand assumes that the numerous spirochetes present

³⁰³² O'BRIEN C S and ALLEN J H Arch Ophth 29 600 1943

³⁰³³ RIEHM W Arch f Augenb 105 55 1931

³⁰³⁴ WESSELY K Muenchen med Wchnsch 58 1713 1911

³⁰³⁶ MAUKSCH H Ztschr f Augenb 91 343 1937

³⁰³⁷ ANNEBERG A R Am J Ophth 21 1265 1938

³⁰³⁸ WOODS A C Arch Ophth 53 321 1924

³⁰³⁹ NOE C A discussion to Kuefer H C et al J Iowa M Soc 31 572 1941

³⁰⁴⁰ DEAN A M DEAN F W and MCCUTCHAN G R Arch Ophth 23 46 1940

³⁰⁴¹ LEMOINE A N ibid 1 66 1929

³⁰⁴² PARLATO S J ibid 14 587 1935

³⁰⁴³ MORAN C T JAMA 102 286 1934

in the corneal tissue of the congenitally luetic infant remain quiescent, while the rest of the organism gradually acquires immunity to the spirochetal antigen, and that any accidental cause, such as minor trauma or infections, will suffice to unite the antibodies and the intra-corneal deposits of antigen, thus evoking a local allergic reaction. While these two theories regard the spirochetes as the antigenic substance, Loewenstein²⁶⁴ champions the opinion that parenchymatous keratitis in the congenitally syphilitic individual is attributable to an auto-endogenous allergy resulting from resorption of altered corneal protein. Nothing more than a slight local trauma or the invasion of the cornea by blood-borne irritants is required to cause the resorption to begin anew, and thus the development of allergic keratitis. That metallergens can also play a causal rôle was demonstrated experimentally by Loewenstein: luetic rabbits responded with parenchymatous inflammation to intracorneal injections of foreign serum.

The results of recent investigations would seem to suggest that patients with tuberculous keratitis are very hypersensitive to tuberculin and that fluctuations in the degree of immunity often parallel the clinical changes. Riehm, Koellner, and others were able to reproduce the disease picture of tuberculous keratitis (as well as conjunctivitis) by means of repeated instillations of tuberculin into the eyes of infected rabbits.

According to Loewenstein, the parenchymatous keratitis developing in the course of long-standing trachoma may be regarded as of auto-endogenous-allergic origin. This group also comprises the inflammations of the cornea, described by Loew and Friedberg, that appear after keratoplasty, iridectomy, and other operations in which injury to corneal tissue occurs, producing alteration of the protein.

Bereston and Baer²⁶⁵ reported 2 cases of bilateral keratoconus (conical cornea) associated with neurodermatitis. In both cases the cutaneous involvement was almost universal, and these authors postulate that the ectodermal allergic changes also affected the cornea, with resultant thinning of the central portion.

Keratoconus may be a hitherto unrecognized ocular complication of severe neurodermatitis.

F IRITIS AND UVEITIS

Throckmorton²⁶⁶ had occasion to keep under observation a case of iritis precipitated by a violent anaphylaxis elicited by the second injection for immunization against typhoid fever. The symptoms disappeared after four weeks and did not recur until sixteen years later, when a second severe anaphylactic shock occurred after administration of antitoxin for laryngeal diphtheria. This corresponds perfectly to the experimentally induced anaphylactic iritis which von Szily²⁶⁷ achieved by means of intracorneal reinjection of horse serum in sensitized animals. But when the reinjection is made into the vitreous or the anterior chamber, the subsequent allergic reaction involves principally the uvea (Kuemmel).

Manifestations of hypersensitiveness can be elicited not only in previously specifically irritated eye structures, but also in sites that have been exposed to nonspecific irritation. Riehm²⁶⁷ demonstrated this in the following way: Rabbits were allergized by subcutaneous injections of horse serum, during the incubation period, the eye was irritated by repeated contusions of the eyeball, so as to produce a traumatic uveitis. Subsequently, after complete retrogression of all manifestations of irritation in the injured eye, intravenous administration of the antigen brought on an allergic uveitis.

It seems likely that allergic mechanisms also play a rôle in those chronic forms of iritis and uveitis, as well as conjunctivitis, that are maintained, continuously or in recurrences, by foci of infection. Riehm assumes that the involved tissues have acquired a special immunologic reactivity to the infectious agents. In support of this assumption, the present writers submit the following clinical observation. A young woman of about 24 years of age had been suffering for a number of years from recurrent episcleritis and conjunctivitis, which had not responded to therapy. Intracutaneous tests produced a very strong reaction to streptococci. The cause of this bacterial allergy was found to be deep-seated suppura-

²⁶⁴ LOEWENSTEIN, A.: *Klin. Monatsbl. f. Augenh.* 82: 64, 1929.

²⁶⁵ BERESTON, E. S., and BAER, R. L.: *Arch. Dermat. & Syph.* 46: 3, 4, 1942.

²⁶⁶ THROCKMORTON, J. H.: cited by Kluver, H. C., et al. *J. Iowa M. Soc.* 31: 372, 1941.

²⁶⁷ RIEHM, W.: *Med. Klin.* 38: 1317, 1943.

tive foci in residual tonsillar tissue radical tonsillectomy completely cured the eye disease

It should be noted that the hypersensitive ness need not necessarily be in relation to bacterial protein in some instances bacterial toxin constitutes the causal excitant Thus Sanders³⁰³ holds that the absorption of bacterial toxin from a distant focus of infection may be responsible for the continued activity of an ocular lesion and even for the initial inflammation If the amount of toxin entering the blood stream is quite massive a definite hemorrhagic lesion may occur (Shwartzman phenomenon) This is especially likely to happen in a highly vascularized tissue such as the uvea Sanders wonders whether the marked vitreous hemorrhage in Eales disease might not be explained on this basis

In addition there are a few additional observations to the effect that intis can be caused by food allergy (Parry³⁰⁴ Roch³⁰⁵) as well as two observations reported by Bothman³⁰² in which dust and mold respectively appeared to be the allergens

Moreover in a number of instances intis secondary glaucoma or acute corneal edema has been observed in patients who were suffering from severe angioneurotic edema (Barkan Kraupa Potvin and Weekers and Barac) Weekers³⁰⁷ called this condition *oedeme al lergique paroxysmique du globe oculaire*

Lastly this group also properly comprises sympathetic ophthalmia and endophthalmitis phaco anaphylactica As to the possibility than these conditions are due to auto endogenous allergy to altered organ specific uveal pigment or to altered organ specific lens tissue the reader is referred to the discussion in the section on auto endogenous allergy (p 124) Sensitization to uveal pigment appears to be present in most cases of posterior uveitis due to focal infection after the disease has been present for a short time This can be shown by intradermal tests with uveal pigment The solution used for this purpose is the so called normal solution a suspension of the pigment from one beef eye in 75 cc of normal saline solution inactivated by heating In sympathetic uveitis or sympathetic ophthalmia focal infection has to be eradicated in conjunction

with desensitization with uveal pigment The latter measure will not succeed if the former condition is not removed (Gill³⁰) The usual pigment solution is employed therapeutically by injecting 0.25 cc daily increasing by 0.25 cc daily until a maximum of 2 cc has been reached at which level it is continued until clinical cure has been attained or the hopelessness of the case definitely established

However this theory of auto endogenous allergy is opposed by a number of authors including Riehm³⁰⁷ who rejects it on the basis of his experimental studies The present status of the problem is approximately as follows There are assumed to be three types of sympathetic ophthalmia in addition to the auto anaphylactic (a) The first is an infectious form due to invasion by certain uveopathogenic micro organisms (b) The second is a tuberculo allergic form Meller³⁰⁷ succeeded in demonstrating the presence of tubercle bacilli by tissue cultures in the eye first affected and assumed that in a tuberculo allergic organism a renewed supply of hematogenously distributed tubercle bacilli leads to local deposition of tuberculo antigen and thus to an allergic focal reaction expressed as a sympathetic ophthalmia it is claimed moreover that not only tubercle bacilli but other foreign protein can elicit such reactions of hypersensitiveness in the eye (c) A third form is seen in association with sarcoma of one eye following regression of the tumor sympathetic ophthalmia develops in the previously unaffected eye According to Riehm³⁰⁷ the uveitis of the second eye is due to an allergic inflammation caused by the release of tumor antigen he explains the selective involvement of the uvea on the basis of the law formulated by himself of elective tissue or organ sensitization

G CATARACT

As early as 1868 cataracts in patients with neurodermatitis were described by Rothmund Thereafter only occasional reports appeared in the literature However since Daniel³⁰⁴ published his 3 cases in this country and stressed the connection with other allergic diseases numerous instances have been re

¹ *PARRY T G W B M J 2 369 1939

² *ROCH M Presse med 45 199 1937

³ *WEEKERS L A h ophth I 769 1937

GILL W D Texas J Med 40 488 1945

*RIEHM W Klin Monats bl f Augenh 88 62 1932

*MELLER J Z h f Augenh 77 1 1932

*DANIEL R K JAMA 10 481 1935

ported (10 cases each by Brunsting³⁰⁷⁵ and Beetham,³⁰⁷⁶ 2 cases each by Sulzberger³⁰⁷⁷ and Appelbaum,³⁰⁷⁸ in addition to many reports of single instances). Up to 1943, according to Carleton,³⁰⁷⁹ a total of 46 cases of cataract complicating neurodermatitis had been reported, to which 2 additional cases were contributed by McDannald.³⁰⁸⁰ Another severe case was recently observed by the senior author. Nearly all these patients had rather severe neurodermatitis, generally acquired in childhood, and some of them had asthma or hay fever as well. Although the skin manifestations usually begin in infancy, the cataract does not appear until later, in the second and fourth decades of life.

It is now generally agreed that these cataracts are analogous to the well-known lenticular opacities caused by certain drugs, such as dinitrophenol, that possess a strong tendency to allergize. The real mechanism underlying the lesions is not known. However, they seem to be a part of the same pathologic process that is responsible for the cutaneous manifestations. It has been suggested that cataract formation may be influenced by the fact that lens and skin have a common origin in the ectoderm. According to this concept, the sensitized skin responds to allergenic influences with neurodermatitic lesions; the sensitized lens capsule, with cataract.

It is suggested that progressive myopia may be on an allergic basis (Wittich⁷⁰⁴).

H. RETINAL ALLERGY

There have been quite a few observations of retinal lesions (macular edema, retinal hemorrhages, and retinal detachment) due to ingested or injected allergens, in patients with angioneurotic edema or urticaria. Coca³⁰⁸¹ was the first to draw attention to this relationship. While Bedell³⁰⁸² and Bothman³⁰⁸³ observed this occurrence following tetanus antitoxin injections, Plumer,³⁰⁸⁴ Prewitt,³⁰⁸⁵ Ba-

lyeat,³⁰⁸⁶ and Pardee³⁰⁸⁷ traced the symptoms to hypersensitiveness to food. Two cases of retinal hemorrhage due to food allergy were mentioned by Wittich.⁷⁰⁴ Bienstock³⁰⁸⁸ reported scotomata, vitreous opacities, and spasms of the retinal blood vessels in himself. He was able to prevent the appearance of these symptoms by elimination of certain animal proteins from his diet, and to reproduce them at will by ingestion of these foods. A similar instance was reported by Berger.³⁰⁸⁹

The senior author had occasion to treat an Egyptian colleague who presented retinal detachment following ingestion of wheat and milk. A propeptan diet served to manage the condition satisfactorily.

Transitory visual disturbances occurring in cold urticaria (Wilder,³⁰⁹⁰ Urbach) are properly to be included in this group only when the latter condition is of allergic origin.

In conclusion it must be stressed that, on the whole, allergic factors are of primary etiologic importance in only a small percentage of the cases of retinal detachment.

I. OPTIC AND RETROBULAR NEURITIS

Optic neuritis is not unusual in severe serum sickness (Mason,³⁰⁹¹ Brown,³⁰⁹² Kennedy³⁰⁹³), and is most likely to be evident when the urticarial eruption is at its height. This condition is also occasionally seen in cases of severe angioneurotic edema. Hayden and Cushman³⁰⁹⁴ reported an isolated case of optic neuritis attributable to food allergy.

While it is evident that a great variety of conditions may cause retrobulbar neuritis, diseases of the paranasal sinuses (infection, allergy, or allergy complicated by infection) may occasionally play an important part (Stark,³⁰⁹⁵ Hansel³⁰⁹⁶). Kennedy³⁰⁹³ described a case of retrobulbar neuritis due to pork hypersensitiveness.

Regarding hemianopsia, intermittent amblyopia, and amaurosis on an allergic basis, the reader is referred to chapter XXVI.

³⁰⁷⁵ BRUNSTING, L. A. *Arch. Dermat. & Syph.* 34, 935, 1936.

³⁰⁷⁶ BEETHAM, W. P. *Arch. Ophthalm.* 24, 21, 1940.

³⁰⁷⁷ SULZBERGER, M. B. *Arch. Dermat. & Syph.* 35, 368, 1937.

³⁰⁷⁸ APPELBAUM, A. *Arch. Ophthalm.* 24, 803, 1940.

³⁰⁷⁹ CARLETON, A. *Brit. J. Dermat.* 55, 83, 1943.

³⁰⁸⁰ MCDANALD, C. E. *Arch. Ophthalm.* 30, 167, 1943.

³⁰⁸¹ COCA, A. *Bull. New York Acad. Med.* 4, 593, 1930.

³⁰⁸² BEDELL, A. J. *New York State J. Med.* 36, 959, 1936.

³⁰⁸³ BOTHMAN, L. *The 1940 Year Book of the Eye, Ear, Nose and Throat*, Chicago: W. B. Saunders, 1940, p. 3.

³⁰⁸⁴ PLUMER, J. S. *Arch. Ophthalm.* 17, 316, 1937.

³⁰⁸⁵ PREWITT, L. H. *Ibid.* 18, 73, 1937.

³⁰⁸⁶ BALYEAT, R. M. *Am. J. Ophthalm.* 20, 580, 1937.

³⁰⁸⁷ PARDEE, J. *J. Nerv. & Mental Dis.* 88, 89, 1938.

³⁰⁸⁸ BIENSTOCK, Maenchen, med. Wochenschr. 79, 101, 1937.

³⁰⁸⁹ BERGER, W. *Wien. med. Wochenschr.* 80, 979, 1930.

³⁰⁹⁰ WILDER, J. *Wien. klin. Wochenschr.* 45, 1458, 1932.

³⁰⁹¹ MASON, V. R. *J.A.M.A.* 78, 88, 1922.

³⁰⁹² BROWN, A. L. *Am. J. Ophthalm.* 8, 614, 1925.

³⁰⁹³ KENNEDY, F. *New York State J. Med.* 36, 469, 1936.

³⁰⁹⁴ HAYDEN, H. C., and CUSHMAN, B. *Illinois M. J.* 80, 500, 1941.

³⁰⁹⁵ STARK, H. H. *J.A.M.A.* 77, 618, 1921.

ALLERGIC DISEASES OF THE EAR

THE allergic diseases affecting the ear may be divided into those involving (1) the external auditory canal, (2) the middle ear, and (3) the internal ear. Our discussion here follows this differentiation.

Dermatitis of the ear canal (and of the auricle) may be the result of hypersensitiveness to drugs used in the treatment of external otitis or otitis media. Furthermore, the condition may be due to allergy to feathers, horse-hair, or kapok, and will disappear when the offending pillows are removed from the bed. Not infrequently, epidermal sensitivity to hair dyes, wave-set lotions, fingernail polishes and other cosmetics will be responsible. In occasional instances, there is a bacterial allergy to streptococci, staphylococci, or fungi, which so commonly inhabit the external auditory canal, this bacterial hypersensitiveness will yield to autogenous vaccine therapy, along with local antibacterial measures. Lastly, Stokes¹⁹³⁸ determined that some cases were due to food allergy, as demonstrated by improvement on elimination diets and exacerbation on ingestion of the allergenic food.

On the basis of 6 painstakingly observed cases, Lewis¹⁹³⁹ was the first to point out that an occasional case presenting the picture of an acute otitis media might be of allergic origin. Proetz¹⁹³⁷ reported similar observations, especially in children under 5 years, and most particularly among weaned, artificially fed infants who proved to be hypersensitive to some ingredient of their formulas. Particularly enlightening is the case of a 15 month old boy who suffered from concurrent middle ear inflammation and asthma, adherence to a diet shown by tests to be innocuous resulted in a prompt cure without any other therapy. Proetz assumes that the ear manifestations are due to recurrent allergic edema of the tympanic cavity and that this condition is much less unusual than is commonly supposed. He holds that it is responsible, when not duly recognized, for many a needless and futile myringotomy.

Jones¹⁹³⁸ reported an instance of otitis media in a child in whom attacks could be induced by ingestion of nuts. Felderman¹⁹³⁹ saw cases of catarrhal otitis media, complicated by mastoiditis, that were markedly improved when the causative food (e.g., egg, milk) was eliminated from the diet.

In 2 cases Noun¹⁹⁴⁰ showed a definite association between chronic otorrhea and specific food hypersensitiveness. The differentiation between swelling of the ear drum due to primary infection and that caused by a specific allergy is of major importance because paracentesis tympani is unnecessary for the latter type and, moreover involves the danger of secondary infection of the middle ear. Swelling of this kind will disappear very quickly on avoidance of the specific antigenic cause or on the use of local medication that shrinks the membrane. Needless to say, an underlying allergy is to be suspected in a middle ear affection chiefly when the patient presents other manifestations of hypersensitiveness.

It should also be noted that allergic states may result in edema of the Eustachian tube, either as an isolated finding, or more commonly in conjunction with such conditions as allergic rhinopathy or hay fever. Such involvement may cause a sense of 'stiffness' in the head, impaired hearing, or earache, and may simulate the symptoms of otitis media or actually result in a catarrhal form of the latter disease. In some cases, secondary infection supervenes, and suppurative otitis media ensues.

In conditions of the inner ear, one is much more frequently justified in suspecting allergy. It has been repeatedly pointed out in the past few years, especially by Leidler and by Kobrak, that the human internal ear can, as a result of circulatory disturbances, present clinical manifestations corresponding to serous otitis interna. In analogy with vasomotor rhinitis, Brunner has suggested the term vasomotor

¹⁹³⁹ LEWIS E. R. *Ann. Otol. Rhin. & Laryng.* 38: 185, 1929

¹⁹³⁷ PROETZ A. W. *ibid.* 40: 67, 1931

¹⁹³⁸ JONES M. F. *ibid.* 47: 910, 1938

¹⁹³⁹ FELDERMAN L. *ibid.* 48: 80, 1936

¹⁹⁴⁰ NOUN L. J. *J. Allergy* 14: 82, 1942

otitis interna. However, in view of the fact that in the strict pathologic sense no inflammation is involved, the senior author³⁰¹⁷ suggested the terms allergic and pathergic otopathy.

The symptoms of this disease can be of varying intensity, ranging from clicking sounds in the ear, isolated tinnitus aurium, slight vertigo, or slight nystagmus, to a clinical picture that includes the most severe attacks of rotary vertigo, nystagmus of the greatest intensity, disappearance of the caloric reaction, marked tinnitus, and definitely reduced hearing, usually of the type of inner- or middle-ear deafness. Moreover, these manifestations are sometimes associated with cerebral symptoms such as incoordination or pareses. Finally, extreme nervousness and irritability may accompany the ear symptoms (Dean³⁰¹¹).

Levy reported a case in which buzzing in the ears could be interpreted as a reaction to dog hair, since elimination of exposure to the animal was followed by freedom from symptoms, while these promptly reappeared when contact with the dog was resumed. Kobrak is of the opinion that at least some instances of "eighth nerve crisis" are of allergic origin. He described a case, for example, in which the patient suffered his initial symptoms during a visit to his goose farm in the country. Proetz³⁰²⁷ observed several cases of labyrinthine reaction—with the picture of sudden irritation of the vestibule as well as cochlear disturbances under certain conditions—that were attributable to food allergy. Among the clinical findings were vertigo, nystagmus becoming more marked on extreme lateral gaze, frequent buzzing sounds in the ear, and a slight decrease in hearing on the involved side. In one of his cases, the patient, a man of 49 years, had been suffering from intermittent ringing and buzzing in the ears, as well as from vertigo, for five years; during an attack, a sharply circumscribed pale elevated edematous spot was found in the nasopharynx. The elimination of milk, butter, and cheese from the patient's diet produced complete freedom from attacks. It is noteworthy that skin tests were of absolutely no value. Jones³⁰²⁸ saw a patient with chronic allergic labyrinthitis in

whom the symptoms disappeared following elimination of milk from the diet.

Criep³¹⁰² and Clarke³¹⁰³ described allergic vertigo. They believe that this condition is due to edema of the structures of the inner ear. The diagnosis is based on the absence of other etiologic factors, on a family history of allergy, and on the presence of other allergic manifestations, as well as on the finding of blood eosinophilia, positive skin tests, and the fact that the vertigo is relieved by injections of epinephrine. Vertigo of allergic origin may occur either as a single isolated symptom or in conjunction with other manifestations, such as tinnitus and deafness.

According to Kuhn³¹⁰⁴ hearing defects are not infrequently due to allergy (4.7 per cent of a series of 1,022 cases). The following symptoms are often noted: fullness of one or both ears, loss of hearing or dullness of hearing; deep dull pain in the ear, itching in the back of the nose and between the nose and the ear; tinnitus, vertigo, or nausea, tightness and drawing sensations or a deep burning in the ear. These very greatly in the same individual as to both presence and intensity from time to time. If the patient obtains subjective relief or if there is improvement in the audiogram readings after a hypodermic injection of epinephrine, allergic investigation is warranted. Eosinophilia of the nasal secretions or blood may be present.

Of the inner-ear diseases, Ménière's syndrome is occasionally of allergic origin; in most of these instances, the allergen is a food. Ménière's syndrome designates a symptom complex characterized by recurring attacks of prolonged and profound vertigo, nausea, and vomiting, and generally accompanied by temporary tinnitus aurium and deafness. The condition is a result of a vasomotor disturbance that can be proved to be of allergic origin in only a few cases. Most instances are considered to be due to a vasospasm on a non-allergic basis (Atkinson³²³), although one-fifth or less of the cases may be the result of a primary vasodilatation, detectable, according to Atkinson,³²² by the skin reaction to an intracutaneous test with histamine (see Fig

³⁰¹¹ DEAN, L. W. Allergic Diseases of the Ear. In Fowler, E. P. (ed.) *Medicine of the Ear*, New York: Nelson, 1939, p. 497.

³¹⁰² CRIEP, L. H. *Pennsylvania M J* 43: 258, 1939.

³¹⁰³ CLARKE, T. W. *New York State J Med* 39: 1498, 1939.

³¹⁰⁴ KUHN, H. A. *J Indiana M A* 36: 143, 1943.

395) His therapy, based on this distinction will be considered below

It was Duke^{210a} who first demonstrated an allergic pathogenesis in 2 of his patients. They did not have the Meniere attacks if they avoided the foods to which they were hyper sensitive (peas and pears in one case, spinach, plums, wine and vinegar in the other). The attacks could be experimentally produced by deliberate feeding of the offending foods or by injection of extracts of these. Similar instances were reported by Rowe and Richet²¹⁷ (fruit vegetable, nuts), Balyeat²¹⁸ (milk, butter, cheese), Atkinson¹⁹⁸ (milk and eggs in one case, milk and beef in another), Dohlman^{210b} (milk, wheat), Dean^{210c} (Crisco), Adelsberger and Munter^{105b} (lobster and alcohol taken together, but not either alone), and Clarke²⁰⁹ (a number of foods as well as kapok, orris root, pyrethrum, and tobacco)

before each meal) made it possible for the patient to partake of these foods with impunity.

In addition there have been reports of cases in which allergens other than ingestants were shown to be the causal agents. Thus Malone²⁰⁷ reported 2 instances one of hyper sensitivity to orris root the other to house dust. Both were cured by hyposensitization. Vandell²⁰⁸ described another case of orris root allergy.

Not all authors concur in the theory of the vasospastic pathogenesis of the Meniere syndrome as outlined above particularly in those cases that are due to allergy. This group holds that there is an alteration in the permeability of the capillary walls in the labyrinth, resulting in local angioneurotic edema. Autopsies on a few such cases have revealed an edema of the semicircular canals or so-called labyrinthine dropsy (Hallpike and

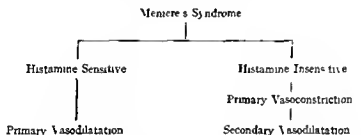


FIG. 395. IDEAL MECHANISM IN MENIERE'S SYNDROME (ATKINSON^{192b})

The senior author observed 2 similar cases. In the first, chocolate was proved to be the eliciting agent. The patient avoided this food and remained entirely free from manifestations for six months. One day he took an amidopyrine suppository for a headache. Half an hour later a typical attack of vertigo started. Subsequent study revealed that the attack had been elicited not by the drug itself, but by the cocoa butter in the suppository.

The second case, which was reported in detail in conjunction with Wilder²⁰⁷ resembled the picture of a cerebellar disturbance, with extreme dizziness and tinnitus aurium. Eggs, pork, and tomatoes were found to be responsible. So long as these foods were avoided, the patient remained free of symptoms. Propeptans in large doses (1 Gm

Cairns²⁰⁹ Lindsay^{210b}) In this connection it is pertinent to note the 3 cases of Dederung²¹¹ as well as the one described by Wilder and the senior author²⁰⁷ for they all presented subcutaneous angioneurotic edema along with Meniere's syndrome.

Dohlman²¹⁰ succeeded in evoking in guinea pigs allergic vestibular disturbances that he localized in the central vestibular zone of the medulla oblongata.

The management of these patients is divided into two phases: relief of the acute symptoms and prevention of future attacks. Unfortunately, oral medication can almost never be

^{210a} DUKE W. W. J. A. M. A. 81: 2179, 1923.

^{210b} DOHLMAN G. Acta oto-laryng. 7: 215, 1939.

²⁰⁷ MALONE J. T. M. Bull. Vet. Admin. 9: 406, 1933.

²⁰⁸ VANDALL H. Southwestern Med. J. 259, 1933.

²⁰⁹ HALLPIKE C. S. and CAIRNS H. J. Laryng. & Otol. 53: 625, 1938.

²¹⁰ LINDSAY J. R. Minnesota Med. 20: 8, 1933.

²¹¹ DEDERUNG D. Arch. f. Ohren, Nasen u. Kehlkopf. 126: 121, 1930.

²¹² DOHLMAN G. Acta oto-laryng. vol. 27 suppl. 32, 1939.

used because of the nausea and vomiting. For the treatment of the acute symptoms, Horton³⁵⁴ highly recommends slow intravenous injection of dilute histamine diphosphate.

TECHNIC A 1 cc ampule of histamine diphosphate containing 2.75 mg per cubic centimeter (equivalent to 10 mg of histamine base), is added to not less than 250 cc of sterile physiologic salt solution and thoroughly mixed. This is then given intravenously by the gravity method. The rate of flow is adjusted so that 28 cc enters the vein every minute, requiring not less than one and a half hours for the 250 cc of solution. The rate of administration is so controlled as to produce no change in the blood pressure or pulse rate. Occasionally the patient will note a slight sensation of warmth in his face, but this can be controlled by reducing the rate of flow. Two or sometimes three treatments are given on successive days.

Since sodium ions cause fluid retention, while potassium ions are diuretic, Peters and Horton³⁵⁵ suggested that the histamine salt be dissolved in an 0.8 per cent solution of potassium chloride, and allowed to flow at a rate of only 10 to 20 drops a minute. These authors observed little or no pain along the course of the vein as commonly occurs when potassium chloride solution alone is given intravenously, particularly at too rapid a rate.

To solve the second phase of the problem, avoidance of the offending foods or other allergens should be strictly enforced. In addition, the Furstenberg³⁵⁶ regimen has been attended with considerable success. This consists of a low-salt diet, along with the administration of ammonium chloride in doses of 3 Gm. (45 gr.) with each meal, three days on and two days off. Thiamin hydrochloride, 3 to 5 mg. (1/20 to 1/12 gr.) three times a day, and nicotinic acid, 50 mg (5/6 gr.) three times a day have also been recommended. If these approaches prove ineffective—or if the allergens cannot be identified—Horton suggests an adequate maintenance dose of histamine diphosphate: 0.275 mg. given subcutaneously two or four times a week for an indefinite period. The dosage should be gradually increased to this point, as outlined on page 228. Employing short courses of intravenous histamine injections, Rainey³⁵⁷ and

Lille, Horton, and Thornell³⁵⁸ reported considerable results in most cases. The latter group noted particular improvement in the hearing. It is recommended that histamine be administered subcutaneously from one to four times a week thereafter for an indefinite period in order to maintain the beneficial results.

According to Atkinson,³⁵⁹ histamine is effective only in the allergic type of Ménière's syndrome. This group responds with a so-called positive histamine skin test, while the nonallergic group fails to do so. The criteria adopted by Atkinson for a positive reaction to 0.01 cc of histamine injected intradermally are a wide area of erythema (1½ to 2 inches, or 3.8 to 5 cm.), a large wheal (½ to ¾ inch, or 1.3 to 1.9 cm.), and the presence of long trailing pseudopodia (1 inch or more in length), all of these appearing within three to five minutes, beginning to fade after twenty minutes, and still apparent at the end of thirty minutes. For a control, the same volume of physiologic saline solution is injected. On this basis, Atkinson³⁶⁰ divides his cases into a primary vasodilatation type, and a primary vasoconstriction type, followed by vasodilatation (Fig 395). He holds that the former is best treated by histamine desensitization, and he prefers the "slow" subcutaneous method. A dose of 0.5 mg of histamine base equivalent is never exceeded and many patients will not tolerate as much. He points out that the second group may appear to be benefited at first by this therapy, since the immediate effect of histamine is vasodilator, but that its ultimate effect, by inducing resistance of the body to its action, is unfavorable (Atkinson³⁶¹). For these cases, he recommends prolonged treatment with niacin (not the amide), at first by intravenous, later by intramuscular injections, and eventually by oral administration. Individualization of dosage is essential, although average peak dosage may be about 50 mg. by injection every second day. This author holds that migraine may be classified on a similar basis.

However, the validity of this concept requires confirmation. The frequent occurrence of strong nonspecific local reactions to histamine, even in nonallergic individuals, makes

³⁵⁴ PETERS, G. A., AND HORTON, B. T. *Proc. Staff Meet., Mayo Clin.* 29, 63, 1945.

³⁵⁵ FURSTENBERG, A. C. *Tr. Pacific Coast Oto-Ophth. Soc.* 21, 159, 1936.

³⁵⁶ RAINY, J. J. *J.A.M.A.* 122: 839, 1945; *New York State J. Med.* 45: 1553, 1945.

³⁵⁷ LILLE, H. L., HORTON, B. T., AND THORNELL, W. C. *Ann. Otol., Rhin. & Laryng.* 53: 717, 1944.

³⁵⁸ ATKINSON, M. *J.A.M.A.* 119, 4, 1942.

the use of this skin test treacherous. More over Farmer⁴⁵ could find no clear evidence of histamine sensitivity as determined by intradermal tests read according to Atkinson's criteria nor any significant difference between an allergic and non allergic group of subjects when the reactions were graded according to less stringent criteria.

Finally surgical intervention may have to be resorted to in instances of extreme and prolonged disability that are utterly intract

able to other forms of therapy although only as a last resort. It may sometimes be difficult to decide on which side the operation is to be performed. Among other approaches that have been employed there may be mentioned section of the eighth nerve (Dandy) injection of alcohol into the labyrinth subtemporal destruction of the labyrinth and electrocoagulation applied by means of a needle introduced into the vestibule (Day¹¹⁸).

¹¹⁸DAY K. M. *Ann Int Med* 23: 41, 1944

CHAPTER XXIX

ALLERGIC DISEASES OF THE CARDIOVASCULAR SYSTEM

THE results of experimental and pathologic studies of the past few years indicate that diseases of the heart and blood vessels are not necessarily to be regarded as invariably due to degenerative processes or to infectious or toxic agents. For it has been proved that, even if in only a small percentage of cases, the cardiovascular system may represent the shock tissue and accordingly respond with allergic cardiac or vascular manifestations that frequently cannot be clinically differentiated from those resulting from organic or functional disturbances. Histologically, on the other hand, each type presents a characteristic picture.

Investigations in this direction have been undertaken almost exclusively along the lines of experimental pathology, particularly by Roessle, Klinge, Rich, and their schools. These investigators demonstrated that repeated injections of nonbacterial allergens in animals can bring about changes in the heart valves, myocardium, endocardium, and coronary vessels, and in the connective tissue of the vascular apparatus. The lesions so produced are identical with those found in the majority of infectious diseases in man (Kaiserling²⁹¹⁹). Kaiserling and Matbies²⁹¹⁰ stress the significance of the neurovegetative regulatory mechanisms in the experimental production of allergic conditions of the vessels. Alterations in the circulation and in the neurovasomotor regulation explain why the injection of antigens into a ligated artery or vein in sensitized animals leads to hyperergic thrombo-arteritis (Migou-nov) or thrombophlebitis (Rinteln) and subsequently to thrombo-angitis obliterans. Similarly, Masugi and Sato²⁹²⁰ succeeded, in sensitized animals, in inducing local allergic tissue damage in the kidney, with the characteristics of glomerulonephritis, by injecting foreign serum into the exposed renal artery and by tightly compressing the artery and renal vein for ten minutes afterward, in order to hold the allergen in the kidney. Following

interference with innervation so as to paralyze vasomotor control, the vasoconstriction and the hyperergic vascular reaction in response to local administration of the antigen ran a far more turbulent course, and similar changes in the kidney could now be produced by way of the general blood stream.

Knepper and Waaler²⁹²¹ demonstrated that physical overtaxation—for example, having the sensitized animal run on a treadmill—will, when even small doses of antigen are injected, cause the vessels of the heart to present hyperergic changes of the nature of arteritis—that is, the antigens circulating in the blood react with the antibodies principally in a site that is a *locus minoris resistentiae*.

Lastly, Roessle²⁹¹⁸ pointed out that in allergic diseases there are many variations of allergic vasculitis, ranging from capillary changes to endarteritis obliterans, periarteritis nodosa, and pulmonary artery sclerosis. These are especially frequent in patients with rheumatic fever. The experimental evidence that rheumatic carditis and rheumatic arteritis, including involvement of the coronary arteries, may be based on phenomena of hypersensitivity will be presented in chapter XXXI.

A. HEART

Hypersensitivity of the myocardium was demonstrated by Seegal and Wilcox.²⁹²² Rabbits' hearts sensitized by injection of egg white into the pericardial sac were perfused with Locke's solution and tested by addition of egg white to the fluid. A characteristic anaphylactic response occurred, in the form of a decrease in the rate of flow of the perfusion fluid through the heart. Wittich²⁹²³ actively anaphylactized chick embryo hearts. The anaphylactic response consisted in a marked slowing of the heart rate and cardiac arrest in diastole. Hyposensitization resulted, as proved by the lack of response following the addition

²⁹¹⁹ KAISERLING, H. Med Welt 10: 1297, 1936

²⁹²⁰ MASUGI, M., and SATO, Y. Virchows Arch. f. path. Anat. 293: 615, 1934

²⁹²¹ KNEPPER, R., and WAALER, G. Ibid. 294: 587, 1935

²⁹²² SEEGAL, B. C., and WILCOX, H. B., Jr. Arch. Path. 30: 416, 1930

²⁹²³ WITTICH, F. W. J. Allergy 12: 523, 1941.

of more antigen. Electrocardiographic studies of the isolated heart showed decreased amplitude and slowing of the action. The occurrence of conduction disturbances in animals during anaphylactic shock, ranging from slight delay to partial and complete heart block as well as auricular and ventricular fibrillation has long been recognized. Creep³¹²⁴ suggested that the electrocardiographic changes found in guinea pigs and rabbits during anaphylaxis may be due to myocardial anoxia.

Harkavy³¹²⁵ proffered the hypothesis that syndromes dependent on vascular reactions in the myocardium, pericardium, and other serous membranes, expressed by cardiac insufficiency, constrictive pericarditis or polyserositis may be attributed to an allergic mechanism, since such polymorphous reactions are sometimes found to accompany asthma.

1 CARDIAC ARRHYTHMIA

Balyeat,¹⁸⁷⁰ Tuft,¹⁴² and others have reported simple tachycardia or extrasystoles due to hypersensitiveness to certain foods; the condition improved upon dietary restriction and recurred when the foods were again ingested. Duke¹⁶⁰¹ described cardiac arrhythmia in some patients sensitive to heat, cold, or exertion; these cases responded favorably to epinephrine. Furthermore, isolated observations of paroxysmal tachycardia due to an underlying allergy have been made (Thomas and Post,³¹²⁶ Wittgenstein,³¹²⁷ Mussio Fournier³¹²⁷). However, the relationship may be considered as definitely established only if—as in the cases recorded by Luria and Wilensky³¹²⁸ and by Harkavy³¹²⁹—elimination of certain foods from the diet restores the cardiac rate to normal, while the heart action is again accelerated on renewed ingestion of the given food. Fifteen allergic patients with paroxysmal tachycardia, including 4 with electrocardiographic evidence of auricular paroxysmal tachycardia and 1 with attacks of auricular paroxysmal tachycardia, auricular fibrillation, and auricular flutter, were studied by Davison

et al.³¹³⁰ The symptoms were relieved in 7 cases by elimination of the offending foods along with treatment for inhalant allergies. Other arrhythmias reported include bradycardia with a relative prolongation of the PR interval and sinus tachycardia interrupted by sinus block with a complete momentary cessation of heart action due to foods (Pantolimi³¹³¹) and nodal rhythm and bundle branch block after 5 grains of acetylsalicylic acid with reversion to normal the following day (Bloom and Walker³¹³²).

The writers treated a young man who regularly suffered from paroxysmal tachycardia following ingestion of milk, butter, or cheese; administration of the appropriate propeptans served to control the condition completely.

2 ANGINA PECTORIS

Although it is by no means the writers' intention to present angina pectoris as an allergic manifestation, it may be said, on the basis of fairly abundant material in the literature, that allergically induced spasm of the coronary vessels can be a cause of this disease, even if only in a small percentage of cases. Lichtwitz³¹³³ was probably the first to attribute a case of angina pectoris to hypersensitivity (to fish); he succeeded in preventing attacks by administering peptones. Similarly, Werley,³¹³⁴ Bienstock,³⁰⁸⁸ von Eiselsberg,³²³⁴ Adelsberger,³¹³⁵ Dattner³⁰⁰⁰ and Funck³¹³⁶ were able to demonstrate the responsibility of foods for typical attacks of angina and to prevent symptoms by eliminating the given foods from the diets. Turnbull³¹³⁷ presented 3 similar patients whose angina was complicated by periodic diarrhea and peripheral venous thrombosis. The senior writer was called upon to treat a physician with severe attacks of angina; found that the condition was due to hypersensitivity to milk and milk

³¹²⁴ CREEP L. H. *Arch Int Med* 48: 1098, 1931.

³¹²⁵ THOMAS W. A. and POST W. E. *JAMA* 84: 569, 1925.

³¹²⁶ WITTGENSTEIN H. *Wien Arch f inn Med* 11: 417, 1925.

³¹²⁷ MUSSIO FOURNIER J. C. *Presse med* 40: 1225, 1932.

³¹²⁸ LURIA R. and WILENSKY. *Deutsche med Wchnschr* 56: 1430, 1930.

³¹²⁹ HARKAVY J. *J Mount Sinai Hosp* 2: 273, 1936.

³¹³⁰ DAVISON H. M., THOROUGHMAN J. C. and BOWDOCK H. *South M J* 36: 560, 1943.

³¹³¹ PANTOLIMI M. *Rev Assoc med argent* 57: 286, 1943.

³¹³² BLOOM N. and WALKER H. *J Lab & Clin Med* 29: 590, 1944.

³¹³³ LICHTWITZ L. *Klin Wchnschr* 4: 2353, 1925.

³¹³⁴ WERLEY G. *J Allergy* 4: 65, 1932.

³¹³⁵ ADELSBERGER L. *Deutsche med Wchnschr* 62: 733, 1936.

³¹³⁶ FUNCK C. *Natürliche Allergie u. der Pathogenese innerer Erkrankungen als nachschaden Erwarbener* ed 2. Berlin: Karger, 1930.

³¹³⁷ TURNBULL J. A. *Am J Digest Dis* 10: 184, 1943.

products, and achieved complete cure by administering milk propeptans.

However, the allergens need not by any means be foods. Thus, Conti¹³³ identified a cresol-containing mustache dye as a causal agent; Shookhoff and Lieberman,¹³⁹ acetylsalicylic acid and, in other cases, ragweed pollen; Puech,¹⁴⁰ digitalis, and Harkavy,^{141,142} tobacco. Lastly, Duke¹⁴⁰¹ described a case in which anginal pain was promptly produced by exposure to heat and was instantly relieved by cold, suggesting a physical allergy as the pathogenic mechanism.

3. MYOCARDITIS (MYOCARDOPATHY)

Sickl¹⁴⁴ assembled 5 cases of interstitial myocarditis complicating dermatitis due to arspenamine. He pointed out that the lesions exhibited eosinophilic exudates similar to those seen in allergic tissue reactions, and advanced the hypothesis that the myocardopathy developed as an allergic response to arspenamine hypersensitiveness of the heart. Brown and McNamara¹⁴⁴ reported a similar case of acute interstitial myocarditis complicating exfoliative dermatitis due to arspenamine. They, too, suspected an allergic etiology. Bahrman¹⁴⁵ examined histologically the heart of a patient who had been hypersensitive to a number of foods and who died during an attack of asthma. He found subendocardial and intramural collections of eosinophile cells in the heart and, in addition, an extensive periarteritis nodosa of the peripheral vessels. In the heart of a patient who died of asthma, Chafee and his associates¹⁴⁶ observed acute diffuse myocarditis with the most marked infiltration of eosinophilic leucocytes.

4. ENDOCARDITIS (ENDOCARDOPATHY)

As is well known, many entirely different kinds of bacteria are capable of producing the same type of valvulitis. The strictly mechanical-bacteriologic doctrine of metastasis ac-

counts for the endocarditis on the basis of the specific characteristics of the bacteria, their number, and the degree of their virulence at the moment. Surely no one would deny the rôle played by bacteria in the production and course of an ulcerative endocarditis, for example; nor would any one overlook the fact that myocarditis can be produced by embolic metastasis of bacteria, although even such simple embolic inflammatory processes are not satisfactorily accounted for by a strictly mechanical explanation. But the concept of simple bacterial metastasis has already proved unacceptable for the pathogenesis of ordinary verrucous endocarditis, since in the great majority of cases no micro-organism at all can be found either on or in the valve tissue. Furthermore, valvulitis has been regarded as the result of strictly toxic damage. There may be some truth to this in certain cases, but it cannot satisfactorily serve as a general explanation for the pathogenesis of a process occurring under any of a variety of conditions.

Endocarditis has often been produced experimentally. On the assumption that bacteria circulating in the blood will find their way directly into the valves during closure, attempts were first made to produce endocarditis by means of intravenous injection of bacteria. This approach failed. Efforts were then made to damage the valves at the same time. This method was only moderately successful. There was a different kind of response, however, when animals were given repeated injections of the same bacteria at definite intervals, along with valvular trauma. Now, for the first time, there were signs of real success. What had happened? The animals had been allergized by preparatory treatment with the bacteria; the resorption of micro-organisms did not, however, take place only in those organs normally having this function—the liver, spleen, bone marrow, and lymph nodes. Instead, the range of resorbing endothelial cells had been enlarged, and those of the endocardium and particularly of the valves also took part in the process of resorbing bacteria. The immunologic response to the infectious agent determines whether a verrucous or an ulcerative endocarditis will develop. A successful defense against the micro-organisms allows the hyaline thrombi

¹³³ CONTI, A. *Atti d. Soc. lomb. disc. med. e biol.* 18, 121, 1929.
¹³⁹ SHOOKHOFF, C., and LIEBERMAN, D. L. *J. Allergy* 4, 506, 1933.

¹⁴⁰ PUECH, *Zentralbl. f. inn. Med.* 54, 126, 1933.

¹⁴¹ HARKAVY, J. *Proc. Soc. Exper. Biol. & Med.* 39, 683, 1933.

¹⁴² Idem, *J. Mt. Sinai Hosp.* 8, 592, 1942.

¹⁴⁴ SICKL, H. *Frankfurt. Ztschr. f. Path.* 49: 283, 1936.

¹⁴⁵ BROWN, C. E., and MCNAMARA, D. H. *Arch. Dermat. & Syph.* 42: 312, 1940.

that form on the valves to organize and scar, producing the verrucous type. In the event of unsuccessful defense the thrombosis increases, and progressive ulcerative endocarditis develops. Therefore according to the present concept, an alteration in the reactivity of the endothelial cells of the valves is essential for the development of endocarditis.

In summary, it can be safely assumed that endocarditis is based on an underlying bacterial allergic process.

We are now also able to understand why horses being treated for the production of immune sera so frequently develop endocarditis, and why this does not happen at the beginning of the immunization, but only later in its course. The first injections allergize the organism, the bacteria being taken up by the endothelial cells of the liver and spleen. As the injections are continued these cells are overwhelmed and the second line of defense including the endothelial cells of the valves, undertakes the same function. This results in endocarditis in the immunized animals (Fig. 396), a pathologic condition well known to those engaged in producing immune sera.

B PERIPHERAL BLOOD VESSELS

1 ESSENTIAL HYPERTENSION

While there is no available evidence to prove or disprove the idea that allergy may be the cause of essential hypertension, there are some reports that would seem to justify this assumption, at least with regard to a limited number of cases. Thus, Waldbott^{31,32} reported a young woman with a systolic blood pressure of 212 mm. of mercury and a diastolic pressure of 115. After a number of food items to which the patient was proved to be allergic had been removed from her diet, the blood pressure dropped to 145 systolic and 92 diastolic after two years; however, it again rose to 195 and 118, respectively, the patient meanwhile having developed hypersensitivity to other foods. Elimination of the latter again served to reduce the blood pressure. Similar cases have been reported by Vaughan and Sullivan,^{33,34} Liston,^{35,37} Gay,^{36,39} Funck,^{31,36}

and Bienstock.^{30,38} According to Price^{10,50} some cases of hypertension are aggravated by food allergy which may be detected by careful experimentation with the diet in conjunction with a study of the pulse record according to the methods outlined by Coca. It is not the total protein content of the diet so much as the specificity of some proteins which is important in this respect, and vegetable proteins are more common offenders than animal proteins.

Feinberg points out that occasional cases of intractable asthma are accompanied by hypertension and that the condition in the latter improves markedly if only temporarily



FIG. 396 ULCERATIVE ENDOCARDITIS IN HORSE REPEATEDLY INJECTED WITH STREPTOCOCCUS ERYSIPELATIS TO PRODUCE IMMUNE SERUM (AFTER BIELING^{20,11})

after administration of epinephrine. Cooke found that such hypertension involved only the systolic level and not the diastolic.

In the present writers' opinion, autoendogenous allergens—that is, substances which are formed in the body and to which the organism becomes hypersensitive—may be assumed to be the cause of at least some cases of hypertension. The demonstration of these substances is, as yet, an extremely difficult matter. Nevertheless attempts should be made to identify them in the urine, for example, in the form of proteoses. It is also conceivable that the beneficial effects of strict diets and particularly of a "starvation

^{31,32} WALDBOTT, G. J. A. M. A. 94: 1390, 1930.

^{33,34} VAUGHAN, W. T. and SULLIVAN, C. J. J. Allergy 8: 573, 1937.

^{35,37} LISTON, O. J. M. SOUTH A. 34: 199, 1927.

regimen" in the treatment of high blood pressure may be due to the elimination of secondary allergens.

2. HYPOTENSION

Hypotension is very common in allergic states (Kahn²¹²) and is not infrequently responsible for the poor general condition of allergic individuals. It may be attributable either to a decreased secretion of epinephrine or to a reduced production of this hormone. Attempts have been made to determine whether the blood of allergic individuals contains less than the normal amount; unfortunately, the available methods of determining epinephrine content are not accurate enough to permit of an answer to this question. The fact remains, however, that many allergic individuals feel much better subjectively when their blood pressure is more nearly normal, and for this purpose small but long-continued doses of ephedrine are valuable. Moreover, adrenal cortical substance (e.g., 2 tablets of cortalex three times a day) may on trial be found to give good results.

A drop in blood pressure has been generally recognized as an expression of a severe allergic reaction, ever since the basic investigations of Widal on the hemoclastic crisis. Moreover, it is an invariable symptom of anaphylactic shock.

3. VASCULAR SPASMS

A considerable mass of evidence suggests that allergically caused vascular spasms are responsible for a number of clinically different disease pictures, the nature of which depends in each case on the portion of the vascular system affected. These conditions include Horton's²¹³ vascular headache (erythromelalgia of the head), certain instances of migraine and epilepsy, and many cases of Raynaud's disease and intermittent claudication. For the sake of brevity, these diseases are discussed in other relevant sections. The intermediation of cold autohemagglutination as a mechanism in reported cases of Raynaud's syndrome, acrocyanosis, and symmetrical gangrene of the tips of the extremities was discussed on

p 136. Here, brief mention will be made only of those periodic attacks of severe pain that appear in patients simultaneously suffering from such allergic manifestations as intermittent bydrarthrosis and angioneurotic edema. In a postmortem examination of a case of this kind, Assmann was able to demonstrate a histologic appearance presumably due to vascular contractions. The condition was assumed to be due to an endogenous allergy.

4. THROMBO-ANGIITIS OBLITERANS

That thrombo-angiitis obliterans occurs chiefly in heavy smokers is a fact that has long been recognized, and the disease had been attributed to the toxic effect of nicotine. In 1933 Harkavy²¹⁰ and shortly afterward Sulzberger²¹¹ suggested the possibility that the deleterious effects might be due not to the nicotine content nor the poisonous combustion products of tobacco but rather to sensitization to tobacco. These authors demonstrated that smokers gave a much higher percentage of positive skin reactions to denicotinized tobacco extracts than did nonsmokers. Friedlander and his associates²¹² reported the occurrence of gangrene of the toes in male albino rats receiving daily peritoneal injections of denicotinized tobacco. These authors believe that they thus reproduced, in animals that had become hypersensitive to tobacco, a disease similar to thrombo-angiitis obliterans. By forbidding the use of tobacco, Harkavy²¹³ and Silbert²¹⁴ relieved patients who gave positive skin reactions to tobacco extracts. Among the other clinical observations which have convinced Silbert²¹⁴ that thrombo-angiitis obliterans is caused by smoking in individuals sensitive to tobacco are the facts that without exception all patients with the disease in his experience have been smokers, and that it is uniformly progressive in those who continue smoking. Harkavy²¹² was able to demonstrate the presence of antibodies to tobacco in the blood of 44 per cent of the cases examined. In addition, both Harkavy

²¹⁰ HARKAVY, J., HEWALD, S., and SILBERT, S. *Proc Soc Exper. Biol & Med* 30: 101, 1932.

²¹¹ SULZBERGER, M. B. *J.A.M.A.* 102: 11, 1934

²¹² FRIEDLANDER, M., SILBERT, S., and LASKEV, N. *Proc Soc Exper Biol & Med* 34: 156, 1936

²¹³ HARKAVY, J. *J Allergy* 9: 473, 1938

²¹⁴ SILBERT, S. *J.A.M.A.* 129: 5, 1945.

²¹² KAHN, I. S. - *M J & Rec* 120, 395, 1924

²¹³ HORTON, B. T., MACLEAN, A. R., and CRAIG, W. M.: *Proc. Staff Meet., Mayo Clin* 14: 257, 1939

and Sulzberger demonstrated hypersensitive ness to tobacco in an appreciable number of patients with angina pectoris and coronary disease

However the contention that hypersensitivity of the vascular system to tobacco is the basic mechanism in thrombo angitis obliterans and coronary disease has been disputed Trasoff³¹⁵⁵ Westcott³¹⁵⁶ and their associates and others found the incidence of positive skin reactions to tobacco to be slightly higher in a control group of nonallergic smokers and nonsmokers than in the group with vascular disease Chobot³¹⁵⁷ elicited reactions even in children Peshkin and Landay³¹⁵⁸ regard the frequently observed positive reactions to tobacco antigen in children to be specific since their blood contained antibodies to tobacco as demonstrated by successful passive transfer tests these authors point out however, that almost all of these children also gave positive skin reactions to pollen They assume that tobacco and pollen possess a common chemical radical and that this satisfactorily explains the hypersensitiveness to tobacco

Thompson³¹⁵⁹ and Naide³¹⁶⁰ contend that peripheral vascular disease resembling if not actually identical with thrombo angitis obliterans may be the result of an advanced degree of hypersensitiveness to dermatophytosis This concept of course requires further confirmation

5 PERIARTERITIS NODOSA

As early as 1866 Kussmaul and Maier described a disease of the arterial walls presenting a peculiar but characteristic histologic appearance and accordingly coined a name for a disease that manifests itself in a protean variety of clinical pictures Gruber³¹⁶¹ stressed the fact that periarteritis nodosa is not a disease entity but is to be regarded as a hyperergic expression involving portions of the arterial walls of one or more organ systems

that have become hypersensitive during the course of a prolonged infectious disease For many years this condition was considered to be a very rare one and was usually seen only post mortem by the pathologist Grant³¹⁶² who wrote an excellent review found that in the seventy four years after it was first described only 350 cases had been reported Nevertheless periarteritis nodosa does not by any means seem to be very rare for a great number of reports on the subject have appeared in the last few years Thus Wilson and Alexander³¹⁶³ found that about 200 authenticated cases were described in the literature from early 1940 through 1943 while Jones³¹⁶⁴ was able to report as many as 14 cases in his own experience And although the etiologic connection with allergy has not as yet been conclusively established the disease is so frequently encountered in association with asthma and other allergic manifestations (Motley³¹⁶⁵ Cohen Kline and Young³¹⁶⁶ Bahrmann³¹⁶⁷ Berger and Weitz³¹⁶⁸ Rackemann and Greene³¹⁶⁹ Trasoff and Scarf³¹⁷⁰ Lebowich and Hunt³¹⁷¹ Coe Reisman and DeHoff³¹⁷² Harkavy³¹⁷³ Baker³¹⁷⁴ and others) that discussion of it in this place certainly seems to be warranted It must be emphasized however, that much of the available clinical material indicates that bacterial allergies are here involved although recent clinical and experimental evidence increasingly suggests that nonbacterial antigens may be responsible These include particularly drugs and foreign serums and rarely foods or pollens

Gruber³¹⁶¹ on the basis of experimental investigations concluded that periarteritis nodosa is a vascular disease caused by cocci in the presence of an underlying allergy and pointed out that the vascular changes occur principally in combination with glomerulo

³¹⁵⁵ TRASOFF A BLUMSTEIN G and MARKS M J *Allergy* 7 20 1936

³¹⁵⁶ WESTCOTT F H and WRIGHT J S *ibid* 9 550 1938

³¹⁵⁷ CHOBOT R *ibid* 6 383 1935

³¹⁵⁸ PESHKIN M M and LANDAY L H *Am J Dis Child* 57 1288 1939

³¹⁵⁹ THOMPSON K W *Yale J Biol & Med* 16 665 1944

³¹⁶⁰ NAIDE M *Am J M S* 202 322 1941

³¹⁶¹ GRUBER G B *Klin Wchnsch* 4 1972 1925

³¹⁶² GRANT R T *Clin Sc* 4 242 1940

³¹⁶³ WILSON A S and ALEXANDER H L *J Lab & Clin Med* 30 19 1945

³¹⁶⁴ JONES G M *Ann Int Med* 16 920 1942

³¹⁶⁵ MOTLEY L J *JA* 31A 106 895 1936

³¹⁶⁶ COHEN M B KLINE B S and YOUNG A M *ibid* 10⁷ 10 1936

³¹⁶⁷ BERGER S S and WEITZ M A *J Allergy* 9 489 1938

³¹⁶⁸ LEBOWICH J and HUNT H D *Am J Clin Path* 10 642 1940

³¹⁶⁹ COE M REISMAN H A and DEHOFF J J *Pediatrics* 15 93 1941

nephritis. Masugi and Isibasi²¹⁷⁰ succeeded in producing periarteritis nodosa in the pulmonary vessels and in the gallbladders of sensitized animals by repeated intravenous injections of *Bacterium coli*. Bahrmann²¹⁷¹ claimed to have induced typical arterial changes in rabbits by repeated large injections of histamine. Selye and Pentz²¹⁷² showed that the lesions of periarteritis nodosa in rabbits are similar to those of malignant hypertension and of rheumatic arteritis, and that each of them can be produced by treatment not only with foreign serums, but with foreign protein of other sorts, as well as with bacterial products and with severe overdosage with desovycortico-sterone acetate. They believe that the development of this disease is merely a response to drastic treatment. Intravenous injection of horse serum into highly serum-sensitized rabbits was found by Rich and Gregory²¹⁷³ to result in arterial lesions typical of periarteritis nodosa, although infarction from vascular occlusion occurred only once, and actual aneurysm formation was not encountered. Acute diffuse glomerulonephritis appeared in a few of the animals.

Numerous authors have attempted to demonstrate a relationship to rheumatic fever. According to Wilson and Alexander,²¹⁷⁴ the two diseases are linked together by three facts: the frequency with which both clinical symptoms of rheumatic fever and typical Aschoff bodies have been found in periarteritis nodosa, the close pathologic similarity between rheumatic arteritis and periarteritis nodosa, and the production of the lesions of both diseases by similar experimental methods. Fox²¹⁷⁵ pointed out that the pathologic lesions resemble those of disseminate lupus erythematosus, and suggests that both conditions may eventually prove to be patterns of reaction to a variety of antigens in hypersensitive persons.

The failure to detect any infective agent in periarteritis, the variety of the clinical symptoms, and the association with blood eosinophilia, urticaria, and bronchial asthma—all

these have led to the belief that the vascular lesion is not the result of a specific disease, but rather the expression of a characteristic reaction of the arterial system, possibly allergic in nature and occurring in the course of varying infections and toxemias. In this connection the observations of Clark and Kaplan²¹⁷⁶ and of Rich²¹⁷⁷ are of special interest: six pneumonia patients who died after severe manifestations of serum sickness due to anti-pneumococcus serum, showed fresh lesions of periarteritis nodosa at necropsy. The majority of Rich's patients had received sulfonamide therapy as well, and the possibility that the sulfonamides can attach themselves to plasma proteins and act as haptens must be considered. In a later review of 8 fatal cases, Rich²¹⁷⁸ found that each had had a definite history of hypersensitive reactions to sulfonamide or serum shortly before death, suggesting a causal relationship. Moreover, since the introduction of sulfonamide therapy there has been a marked increase in the number of cases of periarteritis nodosa coming to necropsy at the Johns Hopkins Hospital. Gibson and Quinlan²¹⁷⁹ reported a case in which the disease appeared to be caused by thiourea employed for the treatment of hyperthyroidism, while Marine and Baumann²¹⁸⁰ observed periarteritis nodosa-like lesions in rats fed thiouracil. Rich²¹⁷⁸ recently reported a patient who had received Lugol's solution and later potassium iodide because of thyrotoxicosis and whose necropsy revealed characteristic lesions of periarteritis nodosa. In this regard it is interesting to recall the older studies of Friedburger and Ito²¹⁸¹ and Jacobs²¹⁸² showing that guinea pigs can be anaphylactically sensitized by a mixture of iodine and guinea pig serum. Here again, as in the case of the sulfonamides, a hapten mechanism comes to mind. All these investigations clearly indicate that these vascular lesions may be a manifestation of allergic hypersensitiveness.

²¹⁷⁰ CLARK, E., and KAPLAN, B. I. Arch. Path. 24: 433, 1937.

²¹⁷¹ RICH, A. R. Bull. Johns Hopkins Hosp. 71: 121, 1942.

²¹⁷² IDEM. Proc. Inst. Med. Chicago 15: 210, 1945.

²¹⁷³ GIBSON, P. C., and QUINLAN, J. T. Lancet 2: 119, 1942.

²¹⁷⁴ MARINE, D., and BAUMANN, S. J. Arch. Path. 39: 325, 1945.

²¹⁷⁵ RICH, A. R. Bull. Johns Hopkins Hosp. 77: 43, 1945.

²¹⁷⁶ FRIEDBURGER, E., and ITO, T. Ztschr. f. Immunopath.-forsch., in press. Therap. 12: 241, 1942.

²¹⁷⁷ JACOBS, J. L. J. Immunol. 23: 373, 1932.

²¹⁷⁸ MASUGI, M., and ISIBASI, T. Beitr. z. path. Anat. u. z. allg. Path. 96: 291, 1936.

²¹⁷⁹ SELYE, H., and PENTZ, E. I. Canad. M. A. J. 49: 264, 1943.

²¹⁸⁰ RICH, A. R., and GREGORY, J. E. Bull. Johns Hopkins Hosp. 72: 65, 1943.

The fundamental pathologic change is an inflammatory lesion involving predominantly the medium sized and small arteries and usually affecting only a segment of the vessel. The condition is characterized by a fibrinoid hyaline necrosis of the media and intima of the arterial wall by exudative processes that fan out from the adventitia toward the media and intima and lastly by formation of granulation tissue consisting of mononuclear eosinophile and neutrophile cells in the adventitia (FIG 397) and healing with scar

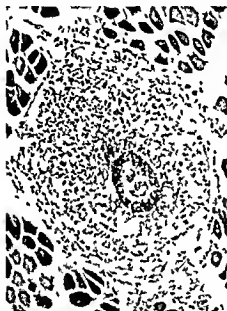


FIG 397 PERIARTERITIS NODOSA ARTERY IN PECTORAL MUSCLE (X 130)

Wall replaced by fibrinoid material in which structural details lost intima swollen vessel surrounded by wide zone of leucocytes chiefly polymorphonuclears (Stain Weigert's elastic and hematoxylin eosin (Courtesy Dr R T Grant)

formation. As a result of these processes the walls of the vessels become considerably thickened and the lumens markedly narrowed (FIG 398). Many of the vessels show thrombosis. Other results of the inflammation of the arterial wall are small aneurysms, rupture and bleeding or infarction. According to current opinion, the presence of both fibrinoid material and a frankly inflammatory cellular reaction is required for a diagnosis of periarteritis nodosa. The veins are never involved.

Clinically the disease is infinitely varied in nature. However the following symptoms are chiefly present: fever, chills, increased sedimentation rate, enlargement of the spleen, leucocytosis, marked eosinophilia, anemia, anorexia, loss of weight, renal symptoms, polyneuritis, polymyositis, and gastrointestinal involvement such as epigastric pain, vomiting, and diarrhea. Some authors stress the point that a bizarre syndrome, particularly if many systems of the body are involved or if accompanied by prolonged fever of unknown

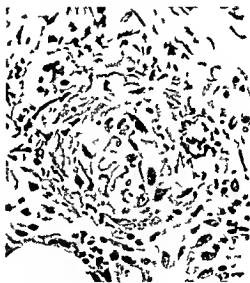


FIG 398 PERIARTERITIS NODOSA ARTERIOLE OF DERMIS (X 400)

Early acute necrosis media replaced by fibrinoid material intima swollen reducing lumen to narrow channel invasion by polymorphonuclear leucocytes (Stain hematoxylin eosin (Courtesy Dr R T Grant)

origin and by leucocytosis and high eosinophilia should suggest a diagnosis of periarteritis nodosa. A hypereosinophilia associated with bronchial asthma should also arouse a suspicion of this diagnosis. In 300 consecutive cases of periarteritis nodosa collected by Wilson and Alexander²¹⁰² bronchial asthma was identified in 18 per cent. All but 3 of 47 cases with asthma showed hypereosinophilia ranging from 11 to 84 per cent, with an average of 53.5 per cent. Only 9 of 151 patients without asthma had hypereosinophilia. The onset of asthma

matic symptoms occurred before the age of 21 in only 11 per cent. If the instances of urticaria, rhinopathy, and other expressions of allergy were included with the asthma, the incidence of allergic disorders accompanying periarteritis nodosa was found to be well over 25 per cent. It is of special interest to note that in about 20 per cent of a series of cases (Schottstaedt²¹³¹), skin manifestations appeared, in the form of urticaria, ecchymoses, nodules, ulcerations, and gangrene of the skin. It is also significant that the combined descriptions of Schoenlein's and Henoch's purpura correspond to a considerable extent with the characteristics of periarteritis nodosa. Thus the preoperative diagnosis in a case reported by Singer²¹³² was Henoch's purpura, and in Baker's²¹³³ case, Schoenlein's purpura. The marked clinical and even histologic similarity between periarteritis nodosa and trichinosis, and the difficulties of differential diagnosis were discussed by Reimann, Price, and Herbut.²¹³⁴ They suggest the possibility that trichinosis may be the primary factor initiating the vascular lesions of periarteritis nodosa through an allergic mechanism. The occurrence of periarteritis nodosa in an infant aged 9 months was reported by Legros²¹³⁵ as diagnosed during life. A positive reaction was produced by a subcutaneous injection of a heated culture of a hemolytic streptococcus from the pharynx, and treatment by sulfapyridine and acetylcholine led to rapid healing of the cutaneous lesions.

The varied symptomatology of the disease is best shown by the syndromes that have been described: Rackemann and Greene²¹³⁶ observed 8 patients in whom severe asthma, pain and numbness in the extremities, hemorrhages in the lungs, kidneys, and bowels, also purpura and an eosinophilia of from 25 to 80 per cent, were proved to be due to periarteritis nodosa. The symptoms in a series of 12 cases reported by McCall and Pennock²¹³⁷ included weakness, myalgia, loss of weight, palpitation, dyspnea, fever, tachycardia, hypertension, and abdominal pain.

Harkavy²¹³⁸ described 7 cases of bronchial asthma due chiefly to bacterial allergy originating from infected sinuses, and associated with recurrent migratory inflammatory interstitial lesions in the lungs, effusions of eosinophils, pericardial involvement, and electrocardiographic abnormalities. These manifestations were reversible and disappeared along with the asthmatic seizures in 4 of the cases, only to recur with recrudescence of the asthma. The presence of eosinophils in the sputum and in the serous exudates, as well as the histologic evidence of periarteritis nodosa in the skin, may be interpreted as expressions of a generalized vascular allergy in the tissues of the body. Involvement of the coronary arteries may produce not only electrocardiographic changes, but also myocardial atrophy, infarction, and fibrosis (Curtis and Coffey²¹³⁹).

Until quite recently it was generally believed that the diagnosis of periarteritis nodosa could be made only post mortem or possibly sometimes when the characteristic histologic picture of this disease was discovered accidentally, so to speak, in the course of a biopsy performed for some other reason, numerous instances have recently been reported, however, showing that physicians are beginning to think of the possibility of such a diagnosis *intra vitam*. Biopsy of a skin nodule or of a tender area in the muscle, usually of the gastrocnemius, pectoral, deltoid, or lateral thigh muscles, will help to confirm or rule out the tentative diagnosis.

Furthermore, a revision must also be made with regard to the prognosis. Until lately, it was generally assumed that the patient could live a year at the very most; now, however, cases are known in which recovery took place. In most of these instances, the patient was left with hypertension and a certain degree of glomerulonephritis.

There is, as yet, nothing like a definite therapeutic approach, since the cause of the disease is not known. In any event, all foci of infection should be combated, and if any offending antigen can be identified after a thorough investigation, it should be eliminated. Patients under sulfonamide therapy should be carefully watched so that the drug may be discontinued on the first appearance of symptoms of hypersensitiveness.

²¹³⁸ CURTIS, A. C., and COFFEY, R. M. *Ibid* 7: 11, 1944

²¹³¹ SCHOTTSTAEDT, W. E. R. *California & West Med.* 36, 186, 1932

²¹³² SINGER, H. A. *Arch Int Med* 39, 865, 1927

²¹³³ REIMANN, H. A., PRICE, A. H., and HERBUT, P. A. *J. A. M. A.* 122, 274, 1943

²¹³⁵ LEGROS, J. *Arch franç de Pédiat* 2: 112, 1945

²¹³⁷ MCCALL, M., and PENNOCK, J. H. *Ann Int Med* 21: 628, 1944

CHAPTER XXX

ALLERGIC DISEASES OF THE HEMATOPOIETIC SYSTEM

A CHANGES IN THE BONE MARROW

HABELMANN^{52, 57} investigations show that allergic reactions may cause typical responses in the leucopoietic bone marrow. These comprise (1) an eosinophilia that is not paralleled by a peripheral eosinophilia and that is independent of the clinical manifestations, (2) a shift in the leucopoietic marrow picture toward a more immature character i.e., the segmented and stab form granulocytes are decreased in proportion to the number of metamyelocytes myelocytes and promyelocytes (3) a marked increase in the number of reticular plasma cells and (4) a definite monocytosis the degree of which is related to the relative severity of the clinical manifestations.

The changes were found to differ quantitatively, depending on whether moderate or very severe allergic states were investigated (Table 63). Habelmann claims that evaluation of the processes in the bone marrow gives a far clearer indication of the existence of allergy than does study of the circulating blood.

Examination of the bone marrow of 16 patients with allergic rhinopathies by Erdstein et al.^{51, 53} revealed very similar changes consisting of intense local eosinophilia with deviation to the left of the eosinophils predominance of myelocytes and promyelocytes over normal leucocytes increase in monocytes and plasma cells and phenomena of local toxicity including nuclear irritation plasma basophilia vacuolation and coarse granulation. The reaction was present both during acute stages of the allergic disease and during periods of improvement. According to these authors the bone marrow reaction is of value for the pathogenic diagnosis of allergic rhinopathies as well as for the differential diagnosis from related conditions.

In a patient with primary pernicious anemia and demonstrated sensitivity to liver extract,

Rynes and Tocantins^{55, 58} speculated that the failure of adequate hemopoietic response which was noted might be due to an allergic reaction of the blood forming organs.

B CHANGES IN THE PERIPHERAL BLOOD

Blood eosinophilia and other blood changes in allergic states was discussed in chapter VII.

TABLE 63—Quantitative Changes in the Bone Marrow in Mild and Severe Allergic States (Habelmann⁵²)

Type of Cells	Percentage Distribution		
	Normal State	Mild Allergic State	Severe Allergic State
Myeloblasts	1.0	1.0	0.8
Promyelocytes	3.4	3.4	10.6
Myelocytes			
neutrophilic	12.4	13.0	20.0
eosinophilic	0.2	0.6	9.0
Metamyelocytes			
neutrophilic	7.0	11.0	14.0
eosinophilic	0.8	4.0	5.0
Band or stab forms			
neutrophilic	33.0	36.0	12.0
eosinophilic	1.4	6.4	3.0
Segmented polymorphonuclears			
neutrophilic	22.0	10.0	5.2
eosinophilic	2.4	3.0	1.0
Lymphocytes	11.0	13.0	15.0
Monocytes	2.0	3.0	7.0
Lymphoid reticular cells	3.0	3.0	5.0
Reticular plasma cells	5.0	4.6	10.4

blood dyscrasias due to drugs in chapter XIV and thrombocytopenia in chapter XXV.

With regard to the hematologic manifestation of hypersensitive states in general, Squier⁵⁹ points out that leucopenia characteristically occurs in allergic reactions and is brought about in part by redistribution of the white cells. However in more pronounced allergic responses there is evidence that the fragility of the leucocyte is increased and that white blood cell destruction occurs. This mechanism is comparable to the lysis of red cells seen in the hemolytic anemia of

^{52, 57} HABELMANN G. *Klin. Wchnschr.* 19: 1231, 1940.

^{51, 53} ERDSTEIN S. F. REV. J. C. and BERTELLI J. A. *Am. Cated. de Pat. Clin. Tuberc.* 4: 284, 1942.

^{55, 58} SQUIER T. L. *Verh. n. M. Month.* 72: 67, 1945.

favism which is recognized to be of allergic origin, and in the hemolysis of transfusion reactions which likewise depends on an antigen-antibody interaction. Allergic reactions may be manifested in the blood by leucopenia, hemolytic anemia or thrombocytopenia, or at times by combinations of these responses. In this connection it is pertinent to recall that leucopenia occurs during anaphylaxis in the guinea pig, dog, rabbit, and pigeon.

A syndrome which might readily be confused with infectious mononucleosis was defined by Randolph and his collaborators.^{102, 110} Atypical lymphocytes, morphologically similar to those seen in infectious mononucleosis, were found in the blood smears. These patients manifested intermittent spontaneous enlargement of the cervical lymph nodes, and sometimes generalized lymphoid hyperplasia. Subjective complaints included unexplained fatigue, unrelieved by adequate rest, weakness, drowsiness, and even deep pains. Allergy to foods appeared to be the most important etiologic factor. The heterophile agglutinin determination was an important aid in the differentiation from infectious mononucleosis.

C. AGRANULOCYTOSIS

The term agranulocytosis is applied to a syndrome that was first described by Schultz,¹¹¹ and that is characterized by severe tonsillitis or pharyngeal or buccal infection, an irregular high fever, extreme malaise, and marked diminution or total absence of granulocytes in the peripheral blood. Although this disease was apparently very rare before 1922, it accounted for more than 1,500 deaths in the United States alone in the years from 1932 to 1934, according to Kracke and Parker.¹¹²

While the earlier investigators incriminated some hidden infection or toxemia, the first intimation that drugs, especially those containing the benzol ring, might be responsible was made by Kracke¹¹³ in 1931, when he described a case of acute fulminating agranulocytosis that appeared after ingestion of large quantities of acetphenetidin. It soon became clear that the disease was occurring with some

frequency in countries such as the United States and Germany, which were being flooded with a variety of synthetic drugs after the last world war. Thus, up to the year 1935 alone, 172 cases were reported in the literature, 153 of them following the use of amidopyrine and the rest attributable to dinitrophenol, organic arsenical compounds, and gold salts. In recent years, according to Long,¹¹⁴ there have been recorded 250 cases due to the various sulfonamide compounds. Among the other drugs which have been reported as causing agranulocytic angina are causalin, allonal, cinchophen, neocinchophen, sedormid, neostibosan, plasmodochin, bismuth, nirvanol, and lately thiouracil.

Schilling¹¹⁵ suggested that this disease might be based on an allergic mechanism, since similar blood findings are obtained in experimental anaphylaxis; and Madison and Squier¹¹⁶ were able to furnish convincing evidence in support of this concept. In almost all of these cases, there is a history of three distinct circumstances. First, the drug was used with impunity for some period of time. Second, there was another considerable period during which the drug was not taken. Third, following administration, after the interval, of even a single small dose, there was a rapid decrease in the granulocytes. Fitz-Hugh,¹¹⁷ Hunter,¹¹⁸ and others also subscribe to the assumption that the changes in the bone marrow and blood in primary granulocytopenia are the result of repeated administration of certain drugs to which the patient has become hypersensitive, and that the clinical manifestations result from secondary bacterial invasion of the tissues owing to the continued granulocytopenia. In a case of severe agranulocytosis due to amidopyrine in rectal suppositories reported by Urbach and Goldburgh,¹¹⁹ the allergization appeared probably to be based on a hapten mechanism. As a result of rapid tissue destruction incident to marked anorexia, protein degradation products (proteoses and peptones) were available for conjugation with the drug, thereby forming a complete antigen capable of allergizing the organism to amidopyrine. The patient recovered following the use of penicillin.

¹¹⁰ RANDOLPH, T. G., and HERRIG, R. A. *Am. J. M. Sc.* 209: 306, 1945.

¹¹¹ SCHULTZ, W. *Deutsche med. Wchnschr.* 48: 1495, 1922.

¹¹² KRACKE, R. R., and PARKER, F. P. *J. A. M. A.* 105: 960, 1935.

¹¹³ KRACKE, R. R. *Am. J. Clin. Path.* 1: 885, 1931.

¹¹⁴ SCHILLING, V. *The Blood Picture*, ed. 7. St. Louis: Mosby, 1929.

¹¹⁵ FITZ-HUGH, T. J. *Ann. Int. Med.* 8: 148, 1934.

¹¹⁶ HUNTER, F. T. *New England J. Med.* 213: 663, 1935.

¹¹⁷ URBACH, E., and GOLDBURGH, H. L. in press.

ALLERGIC DISEASES OF THE JOINTS

A GENERAL classification of joint diseases and a discussion of their nomenclature are beyond the province of this presentation. These may be found in an article¹ recently issued by the Nomenclature Committee of the American Rheumatism Association. We are not interested here in those arthroses that are due to nutritional disturbances, trauma, strains, avitaminosis, endocrine imbalances, metabolic disorders, and certain neurotrophic conditions. We shall also disregard all joint symptoms arising as immediate sequelae to an infection of known etiology (e.g. tuberculosis, gonorrhea, syphilis, influenza) although there may sometimes be an allergic interplay in these conditions owing to previous sensitization of the joint tissues.

In discussing the relationship between allergy and diseases of the joints, two principal types must be distinguished: (a) the strictly allergic arthropathies in which the hypersensitivity itself fully explains all the manifestations relative to the joints; (b) the partially allergic arthropathies in which the allergic component represents only a part of the morbid process in the total complex mechanism.

A STRICTLY ALLERGIC ARTHROPATHIES

1. SERUM DISEASE

As early as 1913, Friedberger and Cederberg demonstrated that reinjection of horse serum into a joint of a specifically allergized rabbit evoked an acute exudative arthritis and peri-arthritis after about four hours. Furthermore, Chini showed that after an injection of a small amount of foreign serum into the knee joint, rabbits responded to a subsequent intravenous injection with inflammatory manifestations in the previously treated knee as well as in other joints.

In serum sickness in human beings, the

arthropathy assumes one of the following clinical forms: (1) a simple arthralgia without objective clinical signs; (2) a manifest non-inflammatory hydarthrosis with periarthral edema; or (3) a condition with all of the characteristics of arthritis such as rubor, calor, dolor, and functio laesa. The disease generally affects several joints and occasionally all of them. The most common sites are the joints of the fingers, then the hand, knee, and shoulder joints.

From the viewpoint of gross pathology, von Pirquet and Schick assumed and probably rightly that the synovial tissue of the joint presents acute transudations like those leading to urticaria in the skin. They based this view on the fact that similar transudations very frequently but not necessarily always appear simultaneously in other organs as well as on the fact that the symptoms are transitory and the return to normal is rapid. Because this condition is not fatal, no post-mortem studies of the human pathology are available in the literature; on the other hand, we are well informed concerning this type of joint disease in animals because the latter frequently receive injections of bacterial protein for the purpose of producing immune serums or are given repeated serum injections for prophylaxis (e.g. against anthrax). FIGURE 399 shows such chronic allergic joint changes in a horse used for production of anti-erysipelas serum.

2. ARTHROPATHY DUE TO RESORPTION OF EXUDATES

When resorption of edema fluid (Gouget and Moreau) of pleural exudates (Bezançon and de Jong) or of blood following auto-hemotherapy (Nicolas Gate) provokes joint symptoms, it may be assumed—provided concomitant conditions suggestive of allergy such as angioneurotic edema or eosinophilia are present—that the picture is that called *arthropathie protéinique* by French authors. This is understood to be the result of allergization by autogenous protein that has become foreign.

¹ "Primer on Arthritis Prepared by a Committee of the American Rheumatism Association," J. A. M. A. 119: 1089-194.

to the organism and elicits an allergic reaction after massive resorption. In other words, this constitutes a type of endogenous allergy

3. ARTHROPATHY DUE TO FOOD OR DRUG ALLERGY

Turnbull,³¹⁹⁹ Weil, de Gennes, and Bezançon,³²⁰⁰ Freund,³²⁰¹ and Adelsberger and Munter¹⁰⁴⁹ observed arthropathies following ingestion of fish, meat, shellfish, egg, cheese, and certain fruits and vegetables, as well as after

been achieved by Adelsberger and Munter,¹⁰⁵⁹ for example. Turnbull³²⁰² has noted that the causative foods are subject to change from time to time in a given case, so that the duration of relief from symptoms on adhering to a strict elimination diet may vary from one year to over eight years. Thereafter, re-evaluation and a different diet are required.

Within this same category are the not rarely encountered joint manifestations in hypersensitivity to neoarsphenamine.



FIG. 399 ADVANCED ARTHRITIS OCCURRING IN HORSE REPEATEDLY INJECTED WITH STREPTOCOCCUS ERYSIPELATIS TO PRODUCE IMMUNE SERUM (AFTER BIELING)

administration of certain chemical substances such as iodide, bromide, antipyrine, and salicylates. Turnbull is inclined to explain these symptoms on the basis of an underlying allergy, since they were consistently found to depend upon the nature and amount of the antigen, and also in view of the transitory and harmless character of the symptoms, as well as of the fact that they were accompanied by urticarial manifestations, which, of course, definitely suggested the existence of an allergy. However, positive proof must depend on deliberate elicitation of the reaction by means of the suspected agent or agents—as has, indeed,

4. INTERMITTENT HYDRARTHROSIS

Numerous authors have observed intermittent transudative joint manifestations, apparently of the most varied etiologies. Among them is a form that, as early as 1903, was regarded by H. Schlesinger as the expression of angioneurotic edema of the joints. When intermittent swellings of the joints occur in association or in alternation with asthma, urticaria, angioneurotic edema, rhinopathy, or migraine (Bolten), suspicion is certainly warranted that the joint involvement is of allergic origin.

This form of joint disease is characterized by periodic swellings of the joints, usually lasting from two to five days and then disappearing completely, only to reappear after a

³¹⁹⁹ TURNBULL, J. A. *J. A. M. A.* 82, 1757, 1924

³²⁰⁰ WEIL, M. P., GENNES, L. DE, and BEZANÇON, F. *Presse méd.* 32, 365, 1924

³²⁰¹ FREUND, E. *Gelenkerkrankungen*. Vienna: Urban, 1929

³²⁰² TURNBULL, J. A. *Am. J. Digest. Dis.* 11, 182, 1944

certain number of days. The intervals between attacks are usually of about the same duration—ten, twelve or fourteen days. The condition often persists for years.

Berger³²⁰³ reported a case in which elimination of the allergens from the diet put an end to the intermittent hydrarthrosis as well as to the concomitant angioneurotic edema and to the gastro intestinal and vasomotor manifestations. Additional instances, most probably of allergic origin, were described by Lewin and Taul³²⁰⁴, Service³²⁰⁵ and Reed et al.³²⁰⁶

Thus, while certain of the joint reactions described above—both those of local allergic nature and also the more or less generalized articular symptoms in serum sickness—represent experimentally reproducible manifestations of hypersensitiveness, other joint diseases may also be of allergic origin. However, this possibility must be definitely established in each case. In such instances sensitization may take place in various ways, through parenteral administration of protein extracts, chronic foci of infection or other and as yet unknown causes, probably of endogenous nature. Either the synovia or the blood vessels of the joint may be the site of the antigen-antibody reaction.

The following approaches are available to determine whether or not a given case of joint disease is allergic in nature (Berger³²⁰⁷).

(1) On the basis of the history and physical examination, an attempt should first be made to rule out any other etiologic possibility (e.g. infectious, endocrine, traumatic). Definitely indicative of an allergic origin of a joint condition is the concurrent presence of typical allergic symptoms in other organs; moreover, the latter may be considered significant even if they do not occur simultaneously with the arthropathy.

(2) The presence of antibodies may be demonstrated by means of skin tests, but preferably by passive transfer. It must be stressed, however, that a positive result demonstrates only that the individual tested is

hypersensitive to the substance in question and the latter need not necessarily bear any etiologic relationship to the joint disease.

(3) Definite proof can be obtained only by means of deliberate elimination and exposure tests.

B. PARTIALLY ALLERGIC JOINT DISEASES

The demonstration of the allergic character of an arthropathy is considerably more difficult in those joint diseases in the etiology and pathogenesis of which both allergic and non-allergic factors are involved.

1. INFECTIOUS ALLERGIC ARTHROPATHIES

There are certain circumstances that have for a long time fostered the suspicion that all arthropathies observed in association with infectious diseases are not necessarily the result of direct bacterial invasion of the joint or joints involved. They include (1) negative cultures from the affected joints, (2) symptomatic similarities to serum sickness (fluctuating character and migratory spread of involvement, healing without sequelae) and (3) symptomatic dissimilarities from the joint changes observed in cases with positive bacterial findings, particularly as regards the presence of pus and occurrence of ankylosis. These considerations gave rise to the hypothesis that primarily nontoxic bacterial antigens entering the blood stream from some focal infection are also capable first of allergizing the joints and then, after a certain period of latency of eliciting an antigen-antibody reaction, the consequence of which is arthropathy (Berger³²⁰⁷). Conclusive proof of this concept has not as yet been furnished and will, for obvious reasons, be difficult to obtain.

Ireberg and Dorst³²⁰⁸ attempted to define an allergic type of chronic arthritis, usually polyarticular, with swelling, local heat and subsequent atrophy of adjacent muscle groups. The involved joints present a fusiform appearance, slight or absent periarticular infiltration, moderate limitation of function, distention with fluid and a characteristic boggy feel on palpation. Roentgenograms show some soft tissue thickening, moderate irregularity and

³²⁰³ BERGER, H. J. A. M. A. 112: 2402, 1939.

³²⁰⁴ LEWIN, P. and TAUL, S. J. b. d. 106: 244, 1936.

³²⁰⁵ SERVICE, W. C. Am. J. Su. 37: 121, 1937.

³²⁰⁶ REED, A. C., CARR, J. L. and ROCHEX, F. Am. J. Trop. Med. 23: 333, 1943.

³²⁰⁷ BERGER, W. Z. i. h. f. w. is. en. h. Baed. k. 3: 134, 1929.

³²⁰⁸ IREBERG, J. A. and DORST, S. E. J. Lab. & Clin. Med. 15: 11, 1930.

narrowing of the joint surfaces, but no extensive newbone formation. Pain is rarely severe and the patients seek treatment because of the appearance of the joints and the limitation of activity. The joint fluid is thin and straw-colored, and the cell content is low, representing chiefly lymphocytes and large mononuclears. The patients show late reactions to skin tests with autogenous vaccines prepared from cultures from foci of infection (teeth, sinuses, tonsils, pharynx, or gastrointestinal tract), and improvement has followed autogenous vaccine therapy. The sensitization of the joint is thought to result either from repeated exposure to soluble toxic products from the distant focus, or from transient bacteriemias during which the joint cavities have been "seeded" with organisms that fail to grow, possibly due to reduced oxygen tension. The former concept is favored by the experimental production of similar lesions in rabbits by means of repeated intra-articular injections of bacterial extract of dysentery bacilli, or by a single injection in animals previously sensitized by the subcutaneous route (Freiberg²⁰⁹).

2. RHEUMATIC AND RHEUMATOID JOINT DISEASES

Under this heading we shall discuss rheumatoid arthritis as well as the arthritis of acute rheumatic fever. While these conditions present distinct clinical pictures, there would seem to be some similarity between the two, according to the recent investigations of Klinge and his school.

Rheumatoid arthritis is a chronic systemic disease of unknown etiology. The joint manifestations consist in the early phases of migratory pains, stiffness, and swelling; in the later stages, of contractures, deformities, and fibrous and bony ankylosis. The condition is usually polyarticular. Many of its clinical features (fever, leucocytosis, increased sedimentation rate, inflammation of the articular tissues, increased synovial fluid of exudative character, and enlarged lymph nodes) suggest that it is an infectious disease. Various theories have been advanced to explain the manner in which rheumatoid arthritis is produced by bacteria. Some hold that the condition is the

direct result of bacterial invasion of the joint; others postulate that specific bacterial toxins emanating from an infected focus affect the joints; and a third school of thought endeavors to show that the disease is due to a reaction between bacterial proteins and the allergized tissues of the joints.

The term *arthritis of rheumatic fever* designates the joint symptoms associated with or secondary to acute rheumatic fever. In this disease, the involvement migrates from one joint to another within a few hours' time, and it does not seem possible that any localized infection could move so rapidly from one site to another. The only logical explanation is that the joint manifestations are due to a toxic or allergic effect from a focus of infection elsewhere in the body, usually the tonsils or heart. However, the presence of an infection does not by itself suffice to account for the rheumatic symptoms, for in subacute bacterial endocarditis, though the blood is filled with streptococci, there is no arthritis, whereas in rheumatic fever, in which positive blood cultures are practically never obtained, many joints are affected (Brown²¹⁰).

While the joint manifestations in typical rheumatic fever do not present any problem in diagnosis, there is a chronic type of rheumatic infection that closely resembles rheumatoid arthritis. The differential diagnosis is made on the basis of the laboratory findings. The blood of patients with rheumatic fever presents significantly elevated antistreptolysin titers, and the streptococcus agglutination test is as a rule negative.²¹¹

Lastly, mention should be made of the syndrome of *palindromic rheumatism*, as described by Hench and Rosenberg.²¹¹ This consists of frequently recurring inflammations of the joints and adjacent tissues, with pain, swelling, and erythema. The symptoms develop in one or two joints within a few hours, last a few days, and then subside completely. The short duration of the symptoms, the absence of sequelae, and the frequent personal and family histories of allergy in such cases, all suggest an allergic etiology to these authors. However, elimination diets, injections of epinephrine, and histamine therapy are not effective.

²¹⁰ BROWN, G. T. J. *Lab & Clin Med* 29: 217, 1934.

²¹¹ HENCH, P. S., and ROSENBERG, E. F. *Proc Staff Meet., Mayo Clin* 116: 808, 1941.

tive (Hench and Rosenberg^{321*}) and evidence of allergy cannot be adduced in every typical case (Cam³⁹¹³). In a series of 1,000 adult patients with asthma, hay fever, urticaria, angioneurotic edema, migraine, gastrointestinal allergy, or allergic dermatitis, Vaughan³²¹⁴ found that about 20 per cent complained or had complained of rheumatic pains. Of these 27 patients stated that the ingestion of certain foods caused exacerbation of their joint symptoms. Thus, in about one eighth of a group of allergic individuals who also had rheumatism or a history of rheumatism, the joint pains could be attributed to allergy.

The theories concerning the pathogenesis of rheumatic fever may be divided into two groups. The one, whose outstanding representatives are Aschoff, Fahr, and Graeff, assumes that a microorganism as yet unknown is the sole etiologic factor involved. In proof of this, these authors regard the rheumatic Aschoff bodies as the expression of a specific reaction bearing the same relationship to the postulated infection as that of tubercles to tuberculosis. However, despite intensive investigative studies, they have not as yet been able to find a specific infectious agent—that is to say, no one has, up to now, succeeded in experimentally reproducing the clinical manifestations of rheumatic fever by injection of so called "specific" bacteria, particularly the often incriminated streptococcus.

On the other hand, Weintraud (1913) was probably the first to advance the theory that the rheumatic fever symptom complex is to be regarded as a special form of reaction of hypersensitiveness caused in the manner in which, for example, tonsillitis leads to sensitization of the body and this, in turn, serves as the basis for a specific rheumatic reaction in response to re exposure to the bacteria entering the blood stream from the tonsils or elsewhere. However, Weintraud incriminates not the bacteria themselves but their toxins.

This allergic hypothesis has, in the past few years, received such strong support, especially from the splendid investigative work of Zinsser and Grinnell,³²¹⁵ Swift, Derick, and Hitch-

cock,³⁹¹⁶ Klinge,⁴⁰² Gudzent,³¹⁷ Bieling,³⁹¹⁸ Rich,³¹⁷⁴ ³¹⁷⁵ and Rich and Gregory,³²¹⁹ that it is now widely accepted. A recent review by Aikawa³²²⁰ summarizes the complex evidence tending to prove a relationship between rheumatic fever and hypersensitiveness. Zinsser and Grinnell³²¹⁵ produced severe allergic reactions in guinea pigs with streptococci and pneumococci, and found a definite parallelism between the hypersensitiveness of the skin and that of the joints. However, they never succeeded in producing joint lesions by means of anything but inoculation directly into the joint. Swift and his associates³⁹¹⁶ by their extensive study of this problem, established proof of the hypersensitiveness of rheumatic patients to streptococcus nucleoproteins. Clawson³⁹²¹ repeatedly injected streptococci subcutaneously in rabbits previously treated with streptococci and in controls not so prepared, while the latter practically never presented Aschoff bodies on autopsy, the pre-injected animals very frequently developed this form of reaction. The important work of Klinge⁴⁰² was based on the concept of hyperergic inflammation as introduced and experimentally corroborated by Roessle. Klinge⁴⁰² Gudzent,³¹⁷ and Bruun³⁹²² made preparatory injections of serum protein containing food extracts, suspensions of killed bacteria and other substances into the joints of animals. They then injected the same antigen into and around the ankle. After one or more such injections hyperergic inflammatory manifestations appeared not only in the synovial membranes and capsules of the joints treated but also in the tendons and other periarticular tissues, as well as in untreated joints. In addition, lesions were found in the arteries, heart valves, myocardium, and skeletal muscles. In other words, histologic evidence was present in all sites where the typical manifestations of rheumatic fever in human beings

³²¹⁵ SWIFT H F, DERICK C L, and HITCHCOCK C H. J A M A 90: 906, 1928.

³¹⁷ GUDZENT F. Ztschr f klin Med 125: 672, 1933.

³¹⁸ BIELING K. Ann d Tomark 26: 26, 1932.

³¹⁹ RICH A R and GREGORY J E. Bull Johns Hopkins 110: p 73, 239, 1933; 75: 115, 1944.

³²²⁰ AIKAWA J K. Ann Int Med 23: 983, 1945.

³⁹²¹ CLAWSON B J. Jb d 4: 433, 1930.
³⁹²² BRUUN E. Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatoid Joint Diseases. London: Oxford, 1940.

³²¹⁴ Idem. Arch Int Med 73: 293, 1944.

³⁹¹³ CAM J C. J A M A 125: 1037, 1944.

³²¹⁴ VAUGHAN W T. J Allergy 14: 256, 1933.

³²¹⁵ ZINSSER H and GRINNELL F. J Immunol 10: 725, 1925.

usually occur. Furthermore, intravenous injection of protein in allergized animals gives rise to the appearance of *microscopic nodules*, in the myocardium and elsewhere, similar to rheumatic granulomas in human beings (Vaubel, Junghans); Roessle⁷ regards these as identical in every way with the Aschoff bodies. We must not fail to mention, however, that Aschoff¹⁷⁰ was every bit as opposed to the view that rheumatic nodules are the expression of an allergic reaction, as he was to the opinion that the clinical manifestations of rheumatism are attributable to an underlying allergy.

Rich and Gregory²¹⁹ advanced additional evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Rabbits subjected to experimental serum sickness, and less often to sensitization with egg albumin, develop in some instances focal cardiac lesions of rheumatic type. These are characterized by focal collagen alteration, Aschoff bodies, focal and diffuse inflammatory lesions, fibrosis in the reparative phase, and valvular involvement. The same experiments resulted in the lesions of periarthritis nodosa in some animals (Rich²¹⁹). The following clinical and pathologic manifestations are common to both rheumatic fever and anaphylactic serum sickness: fever, arthritis, a similar type of synovial exudate, relief of arthralgia by salicylates, cardiac functional abnormalities, urticaria, erythemas, purpura, transient pareses, myocarditis, valvulitis, focal swelling and degeneration of cardiac collagen, cardiac tissue eosinophilia, and inflammatory-necrotic arterial lesions. Moreover, the fact that the peculiar lesion of rheumatic pneumonitis is basically identical with the pneumonitis caused by sulfonamide hypersensitivity in man provides additional evidence that the lesions of acute rheumatic fever may be anaphylactic in origin. Fox and Jones²²⁰ found that most of a series of rabbits surviving anaphylactic shock from horse serum showed pathologic changes, usually limited to the coronary arterioles, closely resembling those of "rheumatic arteritis," and occasionally eosinophilic infiltration of the myocardium. Mild vascular changes were noted less

often in the liver, lungs, testes, kidneys, or mesentery.

According to Selye et al.,²²⁶ overdosage with desoxycorticosterone acetate elicits in rats under certain experimental conditions a polyarthritis which histologically resembles that seen in acute rheumatic fever. In addition, Aschoff bodies in the heart and sometimes periarthritis nodosa were also seen. Joint lesions were more readily produced with desoxycorticosterone acetate in adrenalectomized or thyroidectomized than in intact rats, especially if they were exposed to cold. These authors concluded from these experiments that the adrenal cortex may play an important rôle in the pathogenesis of rheumatic and rheumatoid conditions in man. But Urbach²²⁷ suggested that the results might be interpreted as indicating an endogenous-allergic mechanism.

From the pathologic viewpoint, Klinge recognizes several distinct phases in acute rheumatic fever. The initial rheumatic tissue damage concerns the connective tissue, manifesting itself in a peculiar fibrinoid necrosis of the connective tissue throughout the body, including that of the myocardium. These alterations take the form of swelling (quellung) of the ground substance of the connective tissue, without destruction of the fibrils. This leads in a few weeks' time to the development of the rheumatic nodules, which appear as granulomas characterized by increased fibroblasts and by giant cells with a great deal of cytoplasm. After a while the granulomas retrogress. A scar rich in fibroblasts develops, and is gradually transformed into almost totally collagenous scar tissue.

If a rabbit has been sufficiently allergized by repeated intravenous injections, not only specific but also nonspecific factors, such as the effect of cold on the given joint, will evoke acute or chronic hyperergic manifestations similar to those elicited by injection of the specific allergen directly into the joint. As shown by Gudzent, similar results can be achieved by trauma applied to the knee, for example, either directly or by making the animal jump from a height. In some of his experimental animals, Bruun²²² succeeded in producing inflammatory changes even in the noninjected knee joints. This strongly sug-

²²⁰ Fox, R. A., and Jones, L. R.: *Proc. Soc. Exper. Biol. & Med.*, 55, 294, 1944.

gests, of course, that an allergic polyarthritis may have been produced

Thus, in short, repeated injections of protein, and subsequently the influence of non specific stimuli as well, result in a widespread hyperergic inflammation of the mesenchymal tissues of the body, presenting characteristic localized changes that consist of a degenerative component (a peculiar quelling and waxy necrosis of the connective tissue ground substance) and a proliferative component (proliferation of fixed tissue cells)

It would seem that streptococci play a particularly important rôle in the causation of acute rheumatic fever—not, however, in the sense of a streptococcal sepsis (for one reason, because these bacteria are only extremely seldom found in the rheumatic nodules), but in the sense of an allergy to streptococci. This view receives additional support through various clinical and experimental observations for example virulent streptococci are almost invariably demonstrable in the mucous membranes of the throats of persons suffering from polyarthritis, moreover, many a patient of this type has been completely cured following the removal or elimination of foci of infection. According to Collis, Sheldon, and Hill,²⁴ rheumatic children particularly those with chorea, give stronger skin reactions to hemolytic streptococci than do those not afflicted with rheumatism, during the period of the most active cardiac involvement the skin loses its reactivity, this is regained when the cardiac condition subsides. Adults with rheumatoid arthritis also show a strong tendency to react to hemolytic streptococci and their metabolic products (Traut²⁵). The occurrence of multiple joint pains as evidence of a hypersensitive reaction to one or more immunizing doses of scarlet fever toxin was found by Rhoads and Afremow²²⁶ to be present in a high proportion of persons who had had rheumatic infections or who harbored chronic streptococcus infections which were not present in a control group. Such sensitized individuals appeared, under

observation, to develop rheumatic disorders such as heart disease, polyarthritis and erythema nodosum more frequently. It has also been demonstrated that many patients with rheumatoid arthritis have a high titer of serum agglutinins for *Streptococcus haemolyticus*.

The experimental investigations of Bieling²²⁷ are particularly instructive and significant. He observed that horses repeatedly injected with bacteria, for the purpose of producing immune serum, present all the manifestations characteristic of the category of rheumatoid diseases namely, chronic verrucous endocarditis (see Fig 396), rheumatic myocardial disease, involvement of the skeletal muscles, and severe chronic arthritis and peri-arthritis (see Fig 399).

According to Bieling many different kinds of bacteria can be shown to be allergizing factors responsible for rheumatic diseases in human beings, although it is true that certain micro-organisms—particularly streptococci and tubercle bacilli—are outstanding in this respect. This author points out, however, that the cardiac and joint manifestations are not attributable to the primary properties of these pathogenic agents, but are to be regarded as the expression of a changed reactivity in response to repeated showers of bacteria.

Another manifestation of rheumatic infection is erythema annulare rheumaticum of Lehnendorff Leiner, which is occasionally seen in patients with rheumatic heart disease (Fig 400). The clinical character of the cutaneous lesions (Fig 401) suggests an allergic origin. Other indications are their recurrent nature and the excessive reactions of these patients to peptone injections (Urbach and Bleier²²⁷).

It has been suggested that the favorable effect of salicylates in rheumatic fever may depend on their demonstrated capacity to suppress excess antibody formation in vivo and to alter the antigen antibody reaction in vitro. According to Aikawa²²⁸ it can be stated on good experimental evidence that rheumatic fever is an anaphylactic type of response to some strains of the streptococcus or to their products. It is an antigen antibody reaction. This reaction may be effec

²²⁴ COLLIS W. R. F. SHELDON W. and HILL N. G. *Quart J Med* 1: 511, 1932.

²²⁵ TRAUT E. F. *J Allergy* 8: 501, 1937.

²²⁶ RHODS P. S. and AFREMOW M. L. *Ann Int Med* 19: 60, 1943.

²²⁷ URBACH E. and BLEIER A. *Arch Dermat & Syph* 41: 513, 1950.

tively blocked prophylactically or therapeutically by salicylates which act on the antibody through some yet unknown mechanism." In this connection Bunn²²³ points out that the antibody-antigen reaction appears to occur during a quiescent period (so-called phase 2),

streptococcus or the antigen-antibody reaction has occurred that salicylates or sulfonamides may be effective if given in proper dosage.

The rather marked pathologic and experimental similarities between rheumatic fever on the one hand and disseminate lupus erythe-

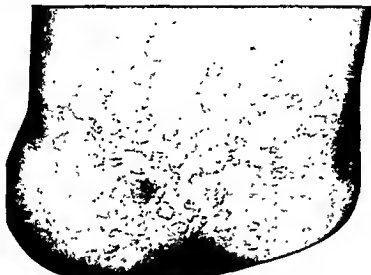


FIG. 400. ERYTHEMA ANNULARE RHEUMATICUM (LEHNDORFF-LEINER)



FIG. 401. APPEARANCE OF LESIONS IN ERYTHEMA ANNULARE RHEUMATICUM (LEHNDORFF-LEINER)

which lasts from a few days to several weeks and which is preceded by several days or longer by infection with group A hemolytic streptococcus or by scarlet fever and followed by the appearance of true active rheumatic fever. It is in the hours before the activation of the

matosis and periarteritis nodosa on the other have already been alluded to. Moreover, not infrequently clinical cases are observed to partake of the characteristics of two or all three of these conditions. The accumulating evidence that each of them may be based on an allergic mechanism strongly suggests

²²³ BUNN, W. H. Ohio State M. J. 41: 1091, 1945

that all these diseases represent reaction patterns to one or more antigens in hypersensitive persons, the nature of the response being determined probably by as yet not understood predispositions.

All the above experimental investigations show that it is possible, by means of intra-articular and/or systemic injections of protein substances (serum, protein containing foods, killed bacteria and fungi, and even nonpathogenic micro organisms) in prepared rabbits and rats, to produce manifestations that resemble, clinically, roentgenologically, and histologically, the conditions observed in the arthritis of acute rheumatic fever and in rheumatoid arthritis in human beings. Not only acute but also chronic hyperergic arthritis can be induced in experimental animals, according to Klinge, in these, after a few months, the picture is quite similar to that of arthritis deformans in human beings. Moreover, as already mentioned, appropriate experimental methods will quite closely reproduce the pathologic lesions of rheumatic carditis and rheumatic arteritis.

This wealth of experimental and clinical observation led Lichtwitz³⁰⁴ to conclude that rheumatic fever is essentially a non infectious disease, but is caused by sensitization to antigens of protein nature, which in most cases are products of micro-organisms, either pathogenic or non pathogenic. The antigens may also include exogenous substances such as horse serum, and the products of the proteolysis that tissues undergo when spent or damaged. Lichtwitz feels that once the rheumatic state is established, any stimulus, such as exposure to cold, may cause a recurrence. It must be pointed out, however, that the vast bulk of clinical observations and careful clinical investigation would tend to implicate the streptococcus and/or its products in the etiology of the disease as well as in its flare ups. Thus, extensive clinical experience convinced Rantz and his associates³⁰⁵ that rheumatic fever is invariably induced by infection with group A hemolytic streptococci, the clinical manifestations resulting from the altered sensitivity of the tissues to products of this organism, although repeated infection with different types

of hemolytic streptococci may be necessary for the development of these disorders. It would appear that the fraction or products to which the tissues are sensitive must be common to all types of group A streptococci. It is suggested that if these substances could be obtained in highly purified form, it would be possible to determine whether they have induced the formation of circulating antibodies and whether the tissues of rheumatic persons are sensitive to them, thereby permitting detection of dangerous streptococcus hypersensitiveness, and possibly leading to preventive or therapeutic measures.

Levinthal³⁰⁶ maintained that acute and chronic rheumatism is an anaphylactic disease with multiple lesions in the mesodermal system produced by continual antigen antibody reactions in or on tissue cells—the antigen consisting of soluble bacterial substances derived from the sites of subacute or chronic infection. The basic cause of rheumatism was thought to be a constitutional or temporary debility of the antibody producing system, with an antibody response insufficient to attain a state of immunity. All agents detrimental to health and the functional integrity of the body, such as disease, malnutrition, exposure, and physical and mental exertion, act as indirect and precipitating factors, interfering with antibody production.

In conclusion it may be said—although conclusive proof is still lacking—that it seems likely, on the basis of the experimental work of Zinsser, Swift, Klinge, and Bruun that rheumatic joint diseases (i.e., those due to rheumatic fever, as well as certain forms of polyarthritis, such as rheumatoid arthritis) may result from the action of bacteria, probably streptococci, in an allergically altered organism. This would again invite the assumption that human rheumatic fever and chronic deforming polyarthritis may be rather closely related. At the same time, it is striking to note the marked histologic and morphologic resemblance between tissue reactions in animals sensitized by purely allergic, non bacterial means (horse serum, for example) and rheumatic tissue reactions in man.

On the basis of these investigations, the proper elimination of all foci of infection is

³⁰⁵ RANTZ L. A. BOISVERT P. J. and SPINK W. W. Arch Int Med 76 131 1945

³⁰⁶ LEVINTHAL W. M. Edinburgh M. J. 50 415 1943

warranted in every case of chronic arthritis. Furthermore, cultures should be made from each of these foci for the preparation of autogenous vaccines and bacterial filtrates, both of which should be used for intradermal tests on the patient; those that elicit reactions should be employed for treatment. Injections are started with a small dose, which is gradually increased according to the local reaction and the symptomatic response. Each dose should be chosen so as to produce a satisfactory local reaction, namely, one that persists on the arm for about forty-eight hours without eliciting any focal or constitutional symptoms. Brown,²¹⁰ Crowe,²¹¹ and Vaughan²¹ stress the importance of small doses in the vaccine desensitization treatment of arthritis, and describe instances in which the condition was aggravated by a too rapid increase in dosage.

Wasson and Brown²²² recently reported very promising results in immunizing children with known rheumatic fever by means of a tannic-acid-precipitated toxin of a specific strain of hemolytic streptococcus, giving four injections at intervals of three weeks each, and then repeating the maximum dose semi-annually. The incidence of exacerbations in the treated group was strikingly lower than that of a control group.

3. GOUT

Our discussion here will concern not the entire disease picture of gout but only the acute attacks. While it is known that both phases are based on an underlying state of hyperuricemia, the elicitation of an acute attack often depends on the intervention of such factors as excessive eating or drinking, exposure, or trauma. The suddenness of the onset, its relationship to certain foods or beverages, and the subsequent complete return to normal of the joints involved—all these factors were interpreted, as early as 1911 (Linossier and Léri; Schittenhelm), as analogous to the joint involvement in serum sickness, or, in other words, as strongly suggesting the possibility of an allergy. The investigators just named, and later Jones, Gudzent,

and others, regarded the attacks on the one hand as attributable to a fundamental predisposition to gout (recognizable by deposits of monosodium urate in the tissues), and on the other, as an expression of hypersensitivity of the joints as well as of the musculature to certain only partially identified substances derived particularly from foods and alcoholic beverages. Moreover, through overexertion, injury, or psychic trauma, the proteins of the muscles, skin, or other tissues may be so altered as to become foreign to the body and thus act as endogenous allergens. In another large group of cases, the attacks appear to be elicited by external excitants such as intercurrent infections, leeches, and mosquito bites (Llewellyn²²³). Kaemmerer²²⁴ hazarded the opinion that the metabolic disturbance commonly known as gout may perhaps bring on a peculiar predisposition of the capillary endothelium of the joints, which thus becomes the shock organ of predilection.

Klinge and Rodriguez²²⁵ reported experimental studies on the relationship of gout and allergy. Injection of 1 per cent sodium monourate into the skin or the joint spaces of normal rabbits was found to produce slight and transitory local reactions. Injection of the same solution into a joint cavity in serum-allergic rabbits engendered a severe arthritis, similar to that produced by injection of the specific serum into the joint. Moreover, injection of the urate solution into the skin or the joint cavities of a specifically sensitized animal increased the intensity of the allergic arthritis evoked by injection of the specific antigen. These authors are of the opinion that gout is predicated on a constitutional disturbance of uric acid metabolism plus an allergic factor. Allergic symptoms such as asthma, hay fever, migraine, urticaria, angioneurotic edema, dermatitis, and pruritus are frequently encountered in gouty individuals and their families.

In a relatively small percentage of cases, the direct responsibility of some food for the attack of gout is apparently demonstrable. Thus, Llewellyn²²³ succeeded in identifying certain kinds of meats, vegetables, fruits, and

²¹⁰ Crowe, H. W.: *J. Lab. & Clin. Med.* 15: 1072, 1930.

²¹¹ Wasson, V. P., and Brown, E. E.: *J. Pediat.* 23: 24, 1943.

²²³ LLEWELLYN, L. J. *Lancet* 1: 475, 1922.

²²⁴ KLEMMER, F., and RODRIGUEZ, H. *Beitr. z. path. Anat. u. z. allg. Path.* 103. 3.9, 1939.

²²⁵ KLINGE, F., and RODRIGUEZ, H. *Beitr. z. path. Anat. u. z. allg. Path.* 103. 3.9, 1939.

also certain grains as the eliciting factors. Vidal et al.^{3,7} demonstrated the role of certain wines notably red Burgundy. These authors point out that the hypersensitiveness involved here is not in relation to the alcohol but rather to certain proteins used for clearing cheap wines. These findings correspond with those of Spillmann and de Lavergue's animal experiments along these lines: guinea pigs preinjected with such proteins responded with anaphylactic shock to reinjection. In another group of cases however the attacks of gout are not elicited by albuminoid substances according to the studies of Vidal, Abram, and Joltrain: the allergen appears rather to be inherent in certain crescences that give the wine its characteristic earthy taste (*qualité de terroir*). Llewellyn believes that the hordein of malt and the ghadin of the other cereals in beer may often be regarded as the causal factor.

On the basis of Berger's^{2,7} conception of gout and allergy and enlarging upon this view we would summarize our present understanding of the subject in the following three points:

(1) An allergic mechanism can elicit an attack of gout.

(2) However the attack cannot be caused by an allergic reaction alone: the patient must also have a predisposition to gout. Therefore the attack is to be regarded as an expression of a partially allergic arthropathy.

(3) In addition to the allergic causes of such an attack there are a number of other etiologic factors some of which belong to the category of nonallergic hypersensitiveness. Furthermore it must not be overlooked that an increased concentration uric acid can in itself—apparently without the mediation of an allergic or pathergic reactive mechanism—be the direct cause of an attack.

It seems possible and even probable that the presence of uric acid in the tissues or in the joints represents the predisposing factor in the development of an allergic arthropathy.

^{3,7} VIDAL, F., ABRAM, P. and JOLTRAIN, E. *Presse méd.* 3: 142, 192.

CHAPTER XXXII

ALLERGIC DISEASES OF THE URINARY TRACT

CLINICAL observations and animal experiments of the last few years have disclosed that, under certain conditions, all parts of the urinary tract may present symptoms of hypersensitiveness. We know this to be true particularly of the kidneys, ureters, bladder, and urethra. It must be borne in mind that the symptoms of urinary tract allergy are much like those of the common urologic diseases. And since allergic conditions involving this system are relatively uncommon, it is incumbent upon the physician suspecting them to establish the diagnosis most carefully, by means of a thorough personal and family history, physical examination, search for associated allergic states, roentgenologic and urologic studies, and clinical pathologic tests, in addition to the indicated allergic approach. Aside from the mechanism of glomerulonephritis, as will be discussed below, the commonest allergenic offenders appear to be foods, particularly wheat, eggs, and milk, but inhalant, bacterial, fungous, drug, and other allergens must be considered.

A. KIDNEYS

Renal disturbances may be suspected of being allergic in origin when they appear simultaneously or alternately with manifestations that are usually of allergic nature, such as asthma, urticaria, angioneurotic edema, or migraine. The assumption of an underlying allergy is further supported when the usual antispasmodic measures fail to bring relief, while an injection of epinephrine is, on the other hand, promptly beneficial, and, furthermore, when there are no calculi or gravel in the urine after the attack of renal colic, but eosinophile cells instead. These renal disturbances manifest themselves not only by pain in the kidney area, sometimes of colicky nature (Duke,³⁰⁰ Rowe,³¹⁰ Miller and Uhle³²⁶), but also frequently by albuminuria, as often occurs in serum exanthems, severe

prolonged attacks of asthma, or following an acute anaphylactic reaction, and occasionally also by hematuria (Coca,³⁰¹ Rhodes,³²⁷ Miller and Uhle³²⁶).

Moreover, kidney symptoms sometimes appear as part of a generalized allergic state. Thus, Adelsberger²²³ described an onset of hematuria following an injection of dust extract in an asthma patient. Kern²⁵³ observed renal manifestations with hematuria and nitrogen retention, together with the classic symptoms of Henoch's purpura, all due to allergy to onion. Thomas and Wicksen²⁵⁹ found hematuria of fifteen months' duration to be related to food and inhalant allergy in one case, and acute hematuria associated with allergic purpura to be precipitated by the inhalation of tar fumes in another—sensitization having presumably taken place some years before from repeated chewing of tar. Osler²²⁷ and Alexander and Eyer-
mann²⁴⁰ reported cases of glomerulonephritis attributable to Henoch's purpura of long standing, the latter condition being considered due to an underlying allergy. In accounting for a case of diffuse glomerulonephritis and severe necrotizing arteriolitis of the entire urinary tract following a revaccination, Herbut³²⁴ favored the hypothesis that these conditions represented an allergic reaction.

Renal lesions, manifested by oliguria or anuria and retention of metabolites usually excreted by the kidney, frequently occur during sulfonamide therapy. These are usually attributed to precipitation of the drugs or particularly their conjugated products, in the urine. However, there is increasing evidence that the kidney may be the site of a hypersensitive type of reaction to these compounds, involving either the tubules or the vascular structures. This occurs more frequently after sulfathiazole than after sulfadiazine or sulfamerazine. Per-

³⁰⁰ DUKES, J. *J. Urol.* 38, 410, 1937.

³⁰¹ ADELSBERGER, L. *Deutsche med. Wchnschr.* 57, 285, 1931.

³¹⁰ ROWE, W. *Am. J. M. Sc.* 11, 628, 1895.

³²⁶ MILLER, M. W., and UHLE, C. A. *W. Internat. Clin.* 3, 153, 1939.

³²⁷ RHODES, J. *L.* and EYERMAN, C. H. *Arch. Dermat. & Syph.* 16, 322, 1927.

³²⁴ HERBUT, P. A. *Am. J. Path.* 20, 1011, 1944.

tinent cases, in which mechanical obstruction was ruled out by means of ureteral irrigations or at autopsy, were reported by Peters and Koven⁸⁴⁴ Dotta and Delporte,⁸⁴⁵ and McClelland⁸⁴⁶ The necropsy studies of Black Schaffer¹⁶⁶ also indicate that the nephrosis appearing under these conditions is a form of anaphylactic renal reaction

Experimental investigations have supported the view that certain renal conditions represent a reaction of hypersensitiveness Halfer and Wolisch⁸⁴⁵ showed in experiments on guinea pigs that during anaphylactic shock the kidneys, and more specifically the glomeruli, presented a diffuse ischemia Particularly striking were a decrease in the number of malpighian corpuscles, glomerular hemorrhages and definite signs of degeneration of the convoluted tubules as well as of the loops of Henle, all of which appeared after about a week

Letterer⁸⁴⁶ demonstrated hyperergic reactions of the glomeruli by exposing the kidney of a frog allergized to serum, sprinkling dried, finely pulverized serum on the glomeruli and then noting the changes in circulation He observed that in allergized animals there was an immediate cessation of local blood flow lasting about one minute—with simultaneous emptying of the glomeruli—while previously untreated animals presented no such reaction, nor did the glomeruli of allergized frogs react when a different dried serum was applied Of particular interest however, are the studies of Masugi⁸⁴⁷ who endeavored to demonstrate that allergic processes in the renal vascular apparatus play a dominant part in the production of acute diffuse glomerulonephritis in man

As early as 1907 Bela Schick broached the assumption that the nephritis of scarlet fever, which becomes clinically apparent as a rule, after the appearance of the exanthem—that is, after a certain incubation period—is to be interpreted as a manifestation of immunity,

or in other words as an allergic reaction of the organism to scarlet fever Friedmann was able to demonstrate the presence of antibodies to streptococcus in the blood of the great majority of individuals convalescing from scarlet fever These theories advanced nearly forty years ago and almost universally considered unsound at the time, have now assumed a highly up to date character in the light of Masugi's experiments

Masugi⁸⁴⁷ injected anti rabbit kidney serum the so called nephrotoxin (obtained by allergizing ducks to rabbit kidney), into the ear veins of rabbits, and produced thereby a diffuse glomerulonephritis with albuminuria cylindruria, increased blood pressure, nitrogen retention, edema, and finally death due to renal insufficiency Histologic examination revealed diffuse involvement of the glomeruli This experimental glomerulonephritis was the result, therefore of the action of immune bodies directed against kidney protein, or in other words of an antigen antibody reaction Needless to say it cannot be assumed that glomerulonephritis in man is attributable to the action of a nephrotoxin as in these animals, however, these experiments do suggest the possibility that allergic mechanisms may play a role in the development of glomerulonephritis in human beings

While these experiments consisted essentially in bringing antibodies to the antigen containing cells, Masugi shortly after carried out an experimental procedure that far more closely reproduces the actual conditions under which diffuse glomerulonephritis occurs in man He first showed in rabbits by repeated intravenous injections of a protein antigen that the kidney is the site of predilection of the subsequent allergic reactions this, he points out, suggests that the kidney is an organ predisposed to allergic manifestations In this connection, the most important responses occurred in the glomeruli, being reflected in an increase in kidney volume, in a peculiar ischemia, and in endothelial proliferation of the glomeruli Masugi then undertook to increase the quantity of the antigen in the kidney circulation by injecting it directly into the renal artery and occluding the renal vessels for some minutes thereafter Under these conditions the glomeruli always presented dif

⁸⁴⁴ PETERS J and KOVEN A J *Ann Allergy* 2 230 1944

⁸⁴⁵ DOTTA J S and DELPORTE T *Rev med de Rosario* 34 436 1944

⁸⁴⁶ MCCLELLAND J C *J Urol* 51 97 1944

⁸⁴⁷ HALFER G and WOLISCH M *Atta d Soc med chir Padova* 8 167 1931

⁸⁴⁸ LETTERER E *Zentralbl f Path* 58 (suppl.) 121 1933

⁸⁴⁹ MASUGI M *Klin Wchnschr* 14 373 1935

fuse involvement in the form of fibrous thrombosis and stasis, changes that might be interpreted as an expression of severe allergic damage.

All this would seem to lend strong support to Masugi's assumption that allergic factors play a decisive rôle in the pathogenesis of acute diffuse glomerulonephritis in man. He also pointed out that this condition is often encountered in association with periarthritis nodosa, which, in all probability, has an allergic pathogenesis. In this connection may be mentioned Rich and Gregory's²¹⁷² experimental findings that acute diffuse glomerulonephritis occurred in some of the rabbits in which lesions of periarthritis nodosa were produced by means of repeated injections of normal horse serum. This lends further support to the view that glomerulonephritis may be due to hypersensitiveness. It cannot be denied, however, that many problems in this domain are still unsolved.

In consideration of the dominant importance generally ascribed to bacteria, especially to streptococci, in the pathogenesis of diffuse glomerulonephritis, Masugi attempted to ascertain whether bacterial antigens are capable of producing experimental kidney diseases. He produced waves of bacteremia by means of repeated injections of *Bacterium coli* or streptococci, and demonstrated that in the course of such chronic infections, and after a phase of apparent nonreactivity, the kidney undergoes tissue changes that strongly resemble acute diffuse glomerulonephritis. Moreover, this pathologic picture was most closely approximated when horse serum or egg protein was used as the antigen. Masugi stressed, however, that the experimental glomerulonephritis produced by bacterial infection is a relatively mild one; he therefore assumed that additional nonspecific factors are involved in human pathology, bringing about a temporary disturbance in the circulation in the kidneys, as a result of which unusually large quantities of the antigen are diverted to the kidney.

While Masugi's findings themselves have been confirmed (Fahr, Hemprich, Weiss), criticism has been directed against the allergic theory, viz., the assumption that the nephrotoxic effects are actually due to an allergic reaction. Aschoff particularly raised the ques-

tion whether the antiserum does not in itself contain a toxic factor that, in a sufficiently strong concentration, might be the cause of the severe kidney damage. However, Ahlström²²¹⁸ as well as Fahr²²¹⁹ has demonstrated that the combined effect of two factors—the one allergic and the other toxic—can produce in animals an acute glomerulonephritis identical with that observed in human beings. These authors showed that renal tissue is normally quite refractory to allergic influences. But a kidney poison—e.g., *staphylococcus toxin*—alters the reactivity to such an extent that subsequent repeated intravenous injections of foreign serum elicit an allergic reaction localized in the kidneys and taking the form of a glomerulonephritis. In close conformity with these views are the findings of Schwenker and Comptoir²⁰⁶ to the effect that most persons suffering from scarlet fever develop circulating antibodies to their own kidney tissues. From these data the authors concluded that streptococcal toxin damages some of the kidney tissue during the primary infection in scarlet fever. The altered kidney proteins thus produced combine with the bacterial toxin to form complete antigens and thereby call forth the production of specific antibodies to kidney tissue, as a consequence of which, they assume, postscarlatinal nephritis ensues. This concept received experimental support in the observation by Kay^{2220a} that the suppression of antibody formation in nephrotoxin-treated rabbits by means of roentgen radiation also prevented the appearance of nephritis, whereas passive transfer of such antibodies from another animal resulted in a prompt onset of nephritis, without a latent period.

Moreover, mention must be made of Swift and Smadel's^{2220b} important contributions. These authors were able not only to bring on nephritis in rats by means of injections of antiserum, but also to prevent the renal damage by injecting rat kidney extract immediately before administering the antiserum intravenously. They believe this to prove that the nephrotoxic action of the antikidney

²²¹⁸ AHLSTRÖM, C. G. *Acta path. et microbiol. Scandinav.*, suppl. 29, 1936.

²²¹⁹ FAHR, T. *Klin. Wochenschr.* 15: 505, 1936.

^{2220a} KAY, C. F. *Am. J. M. Sc.* 204: 483, 1912.

^{2220b} SWIFT, H. F., and SMADEL, J. E. *J. Exper. Med.* 65: 557, 1937.

serum is caused by the presence in the latter of an organ specific antibody namely the nephrotoxin Seegal and Loeb⁵⁴⁶ found that injections of anti placenta serum as well as of anti kidney serum caused a chronic progressive nephritis in rats

Finally Selye and Pentz⁵⁴⁷ showed that administration of desoxycorticosterone acetate in large dosage caused nephrosclerosis with increased blood pressure and disturbances in electrolyte metabolism in various laboratory species In addition to the renal findings Aschoff bodies in the heart and the lesions of periarteritis nodosa were noted—both of which are now considered as expressions of an allergic state Although these authors attributed these manifestations to toxic actions they were elicited by repeated injections of a hormone and may well be due to an endogenous-allergic mechanism (Urbach⁵⁴⁷)

B URETERS

Many an attack of renal calculus in cases in which the presence of a stone can never be proved and many a case of renal colic may on the basis of recent observations be interpreted as an allergic reaction taking place in the ureter This diagnosis seems all the more likely to be correct when the symptoms mentioned occur simultaneously or in alternation with asthmatic or migraine attacks The most conclusive proof is supplied of course when elimination of the incriminated agent such as rhubarb (Adelsberger and Munter⁵⁴⁸) meat and fruit (Gutmann⁵⁴⁹) milk (Litzner⁵⁵⁰) and beer (Urbach) causes the cramp-like pains in the region of the urinary tract to disappear and when these recur after renewed exposure to the suspected substance The diagnosis of allergy receives strong support when the usual spasm relieving measures prove to be totally useless while an injection of epinephrine brings prompt although of course only temporary relief The presence of erythrocytes in the urine is not to be regarded as evidence against the possibility of an allergic origin unless they are present in great numbers

Blaustein⁵⁵¹ examining a case of such severity that it led to anuria observed a marked swelling of the ureteral orifices

C BLADDER AND URETHRA

Allergic reactions in the bladder seem to be relatively frequent According to Duke⁵⁵² painful urination or constant pain in the bladder area without objective findings suggests the possibility of bladder allergy these symptoms sometimes appear as isolated manifestations due for instance to hypersensitiveness to some food (Duke⁵⁵³ Rowe⁵⁵⁴) or as part of a generalized allergic syndrome Thus Salen⁵⁵⁵ points out that during an asthma attack the patient commonly experiences a strong desire to urinate In cases of this kind he found numerous eosinophile cells in the sediment of the sterile urine passed after the attack This strongly suggests allergic involvement of the urinary tract all the more so in view of the fact that the eosinophils could no longer be found after the patients had received anti allergic treatment In addition Rowe describes as the first sign of an allergic reaction following an injection of mule dander a strong contraction of the bladder with involuntary urination—symptoms that incidentally are the rule in severe anaphylactic conditions not only in animals but also in man In a case of this kind Blaustein⁵⁵⁶ found the bladder mucosa to be edematous and pale

At this point brief mention should also be made of the disease picture of colica mucosa of the bladder which Vogl⁵⁵⁷ described and which is probably of allergic origin The case was that of an elderly woman who had been suffering for twenty five years from recurring mucous colitis (evacuation in the stool of long stringy membranes sometimes as many as forty in a day) and also from a spasmodic cough with expectoration of long rolled up strings of mucus This patient was suddenly afflicted with a cramplike pain in the bladder and a distressing urge to urinate the urine was found to contain tattered grayish white membranes some as large as the

⁵⁴⁴ GUTMANN M J M d Welt 4 730 1930

⁵⁴⁵ LITZNER S Med Klin 32 630 1936

⁵⁴⁶ BLAUSTEIN J U I 16 39 1926

⁵⁴⁷ DUKER W W Ann Int Med 1 117 1922

⁵⁴⁸ VOGEL A Wochschr Wchsch 48 756 193

palm of a hand. This condition persisted for twenty-four hours. Regrettably, allergy tests were not made. A similar case was observed by Litzner²⁵²; after ingestion of flour and milk, the urinary sediment was found to contain strikingly numerous eosinophile cells, because of which the author coined the designation "eosinophile cystitis."

Thomas and Wicksten³³⁹ reported a number of pertinent cases: urinary frequency and painful urination caused by paint fumes, dysuria and cystitis from the same cause; frequency and nocturia from ingestion of eggs and beer, frequency, tenesmus, and cystitis caused by corn and celery; dysuria and tenesmus following ingestion of aspirin and acid fruits; and a Hunner's ulcer aggravated by chocolate or grapefruit juice. Many of these patients had other unquestionable allergic conditions, and relief was afforded by avoidance or elimination of the causative allergens, and other appropriate allergic therapy. While eosinophils were frequently found in the urine, they were not consistently present, especially when bladder symptoms were prominent.

Finally, Bray's¹⁹ important studies remain to be considered here. According to these investigations, some cases of enuresis are attributable to allergy. Bray himself encountered this symptom in 5 per cent of his cases of allergic children. He points out that the innervation of the bladder is quite similar to that of the lungs: the cranial portion of the parasympathetic system supplies the lungs, and its sacral division the bladder, with constrictor nerves, while both the bronchi and the sphincter of the bladder are influenced in the opposite way by the sympathetic nerves.

Bray divides the cases into three groups. The first is characterized by the appearance of bedwetting in association with other typical allergic manifestations, such as asthma, hay fever, dermatitis, migraine, or lichen urticatus. He presents a number of examples showing that identification (generally by means of skin tests) and elimination of the allergen may result in the cure of an enuresis of many years' standing as readily as of an asthmatic condition. He observed cases in which the allergens were foods (wheat, pork, eggs), feathers, horsehair (in pillows and mattresses), and even cold water. Furthermore, there is a

variant in that in occasional instances the bedwetting and the associated allergic disease are not caused by the same allergen. In the second group, other typical allergic manifestations are not present, but there are certain relationships permitting the assumption that the cases are of allergic origin—for example, when the bedwetting occurs only in association with bronchitis or a cold due probably to bacterial allergy, or only at certain times of the year, such as spring, suggesting the possibility of pollen hypersensitiveness. Lastly, Bray was able to demonstrate, by means of tests, the existence of an underlying allergy in a number of cases in which enuresis was the only symptom. In any event, it is advisable, when the usual therapy (fluid restriction, belladonna, habit training) fails, to perform allergic tests and to determine the effect of epinephrine. Kittredge and Brown²⁵⁶ reported excellent results from the administration of a single dose of 50 mg ($\frac{3}{4}$ grain) of ephedrine sulfate each night at bedtime in a series of children who were chronic bedwetters and in whom urinary infection, mechanical obstruction, neurologic defect, and mental retardation were not present.

The absorption of unaltered allergenic protein from the urinary bladder in monkeys and human beings was demonstrated by Baretz, Harten, and Walzer.²⁵⁷ Skin sites passively sensitized with human serum containing antibodies for cottonseed reacted within a few minutes after cottonseed extract was introduced into the bladder.

However, not only the bladder but also the urethra can react allergically. Thus, Rattner²⁵⁸ described nonspecific urethritis, along with balanitis and with dermatitis of the prepuce and shaft of the penis, appearing shortly after a new type of condom had been used. Skin tests with this were positive, and the urethritis disappeared when this contraceptive was no longer employed. In other cases, allergic urethritis may be a part of a generalized hypersensitiveness. Froboese, for example, described a nirvanol exanthem ac-

²⁵⁶ KITTREDGE, W. E., and BROWN, H. G., *New Orleans M. & S. J.* 96: 562, 1944.

²⁵⁷ BARETZ, L. H., HARTEN, M., and WALZER, M. *J. Urol.* 50: 71, 1943.

²⁵⁸ RATTNER, H. *J. A. M. A.* 105: 1189, 1935.

accompanied by enanthems of the mucosa of the mouth and urethra

D HEMOGLOBINURIA

The condition of paroxysmal hemoglobinuria has been discussed in the section on endogenous allergy, since in all probability it is an autoanaphylactic manifestation. In this connection it may be of interest to note that paroxysmal hemoglobinuria has been observed in conjunction with cold urticaria by Bray⁷⁹ and by Richl and Risak.^{79b}

Furthermore, McCrae and Ullery^{79c} and Hutton^{79d} reported cases of favism (hyper-

sensitiveness to the bean *Vicia faba*) presenting systemic reactions including hemoglobinuria. Skin tests with an extract of fava bean in a 1:1,000 dilution, were positive, and were followed by malaise and backache persisting for four days.

Fernán Núñez⁸⁰ is of the opinion that acute exacerbations of hemoglobinuric fever accompanying infestation with *Plasmodium falciparum* are comparable to anaphylactic attacks. He bases his assumption that black water fever represents an allergic response to the plasmodia on the fact that intracutaneous injections of killed plasmodia elicited positive reactions only in individuals who had had the disease.

^{79a} RIEHL G. JA. and RISAK E. *Ztschr. f. klin. Med.* 124: 29, 1933.

^{79b} McCRAE T. and ULLERY J. C. *J. A. M. A.* 101: 1389, 1933.

^{79c} HUTTON J. E. *ibid.* 104: 1618, 1937.

⁸⁰ FERNÁN NÚÑEZ M. *Am. J. Trop. Med.* 16: 553, 1936.

CHAPTER XXXIII

ALLERGIC MANIFESTATIONS DUE TO FUNCTIONAL AND PATHOLOGIC CHANGES OF THE FEMALE GENITAL ORGANS

IN THE section on predisposing factors in allergy, the relationship of menstruation, the menopause, and ovarian dysfunctions to allergy was discussed. Examples were presented showing that certain foods, for example, or sunlight, may exert an allergenic effect only during the menstrual period. At this point, on the other hand, discussion will be devoted to those allergic and pathergic conditions that are produced by specific substances formed within the body of the menstruating or pregnant woman.

Parenthetically it may be noted that the absorption of allergenic protein from the uterine cervical canal and less constantly from the vagina was demonstrated by Rosenzweig and Walzer.³²³ It is therefore necessary to bear in mind the possibility not merely of local effects but of distant allergic responses caused by medication and contraceptive preparations in contact with the vagina or uterine cervix.

A. MENSTRUATION

Shortly before or during the menstrual period, very many women suffer from one or more manifestations that disappear either immediately or within several days after the cessation of menstruation. These include cutaneous lesions (acne, herpes, urticaria, dermatitis, erythema, and vulvar pruritus), migraine or migraine-like headaches, nausea, vomiting, rheumatoid-neuralgic symptoms, and asthma. So-called premenstrual tension, beginning in the last week prior to menstruation and ceasing with the onset of bleeding, is characterized by emotional instability, nervousness, irritability, depression, sleeplessness, abdominal distention, subcutaneous edema, feeling of tightness of the skin, cramps, and occasionally bizarre manifestations such as premenstrual coma or convulsions. Even such phenomena as the wilting of plants or

flowers in the hands have been described as occurring in some women at the time of menstruation.

Such symptoms—some of which are merely disagreeable, while others are downright incapacitating—have been explained in many different ways. Frank³²⁴ suggested that these conditions are due to an increased concentration of estrogenic substances in the blood, and therefore recommended the administration of progesterone (1 to 5 mg., two or three times during the week or two weeks preceding the menses), while others have employed androgens. In direct contrast to this view, Schoelke³²⁵ holds that at the time when the symptoms are most severe (immediately before menstruation) the ovary is producing little estrogenic hormone, and when large amounts of this hormone are administered, they subside. Still other authors have advanced the hypothesis that premenstrual tension especially is due to an increase in extracellular fluid in various tissues, such as the brain, skin, and gastro-intestinal tract. On these grounds, the patient is given 1.0 Gm. (15 grains) of ammonium chloride three or four times a day, beginning in the midmenstrual interval and continuing until the beginning of menstrual flow, the aim being to combat the increase in extracellular fluid; at the same time, she is advised to avoid table salt and sodium bicarbonate. While the hydration of the tissues and the hydermia are well-established facts, they are merely symptoms of the premenstrual physiologic changes and not the real causes of these

Aside from the hormonal and chemical theories, there are two others, the toxic and the allergic.

No less an authority than Schick³²⁶ attempted to demonstrate the existence of a menstrual toxin, in order to confirm the old

³²³ ROSENZWEIG, M., and WALZER, M. - *Ann. J. Obst. & Gynec.* 43: 286, 1943

³²⁴ FRANK, R. - *Bull. New York Acad. Med.* 17: 854, 1941.

³²⁵ SCHOELKE, K. H. - *Deutsche med. Wchnschr.* 67: 842, 1941

³²⁶ SCHICK, B. - *Wien. med. Wchnschr.* 70: 938, 1920

deeply ingrained popular view that a poison is produced in the female body during menstruation. However, this distinguished investigator—and later, others who worked in this same field—was unable to demonstrate anything like a chemically definable toxic substance in the blood or in the discharges of the menstruating woman. They arrived at the conclusion, therefore, that the "menstrual toxin" is nothing more than a premenstrual increase of substances of hormonal derivation originating from pathologic processes in the corpus luteum (Géber⁵²⁰) or in the endometrium (Salén⁵²²), and, when produced in sufficiently large quantities, causing the clinical symptoms noted.* The question then arises as to whether these substances are to be considered as of endogenous toxic or endogenous allergic origin.

The writers⁵²⁷ are of the opinion that in principle both possibilities must be granted. We favor the postulation of a hormonal endogenous allergy (1) when, as in cases of menstrual urticaria, attacks can be provoked in the patient, but not in controls, by injection of premenstrual serum during the intermenstruum (Géber,⁵²⁰ Lichter,⁵²¹ Salén⁵²²), (2) when local wheal reactions can be elicited only with the patient's premenstrual blood and only in the patient herself (Urbach⁵²⁷), (3) when passive transfer of the hypersensitivity to the menstrual secretion is possible (Salén⁵²²), or (4) when, as in Waldbott's⁵¹³ case, the patient, who experienced an anaphylactic shock following an injection of estrone (theelin), thereafter regularly had urticaria and asthma shortly before each menstrual period. (For a more complete discussion, see the section on endogenous allergens.)

Zondek and Bromberg⁵²⁶ presented evidence on the basis of positive skin tests and passive transfers that many menstrually related conditions represent a true endocrine allergy. Thus, they elicited positive intradermal reactions with synthetic steroid hormones in 75 per cent of a group of cases of premenstrual

tension. Likewise, Phillips⁵²⁸ found that some women with premenstrual headache, sometimes associated with nausea vomiting, vertigo, visual disturbances, and even pruritus or urticaria, gave sharply positive reactions to intradermal testing with a 1:5 dilution of synapoidin (a combination of chorionic gonadotropin and pituitary extract). Symptomatic relief was afforded in those with positive reactions by intradermal desensitization, ranging from 0.02 cc to 0.3 cc of a 1:5 dilution in 5 per cent dextrose. Similar results were obtained in women with premenstrual migraine and tension. Unexpectedly, two patients were freed of dysmenorrhea, and two noted improvement of acneiform rashes appearing before their periods.

The assumption of an allergic origin is supported above all by the fact that the disturbances incident to menstruation can be cured by systematic injection of serum taken during the premenstrual exacerbation of the cutaneous lesions, migraine, asthma, or other symptoms. For this purpose, the writers employ the method introduced by Geber.⁵²⁰ About 20 cc of the patient's blood is withdrawn at this time under aseptic precautions and centrifuged, and the sterile serum is preserved with 1:10,000 merthiolate in rubber-stoppered vials at refrigerator temperatures. The patient is given 0.2 cc of serum every other day during the intermenstruum. The injections are carried out according to the depot method of Lehner and Rajka; namely, four successive intracutaneous injections are given in the same site. Favorable results have been reported by Malinin,⁵²⁹ Harrison,⁵³² Hopkins and Kesten,⁵³⁴ Cameron,⁵³⁵ and the writers.⁵²⁷ Salén⁵²² employed menstrual discharge collected during the first hours of menstruation, before it becomes definitely sanguineous.

There can be no doubt that, of the menstrual disorders of this type, cutaneous manifestations are the most common. Schoelzke⁵⁴⁵ noted such skin conditions in about 38 per cent of all women between the ages of 14 and 50 years. Acne vulgaris is the most frequently encountered. While this condition often consists only in the appearance of iso-

* Jahn⁵²³ suggested another interesting mechanism to account for these cases. He postulated that reflux of menstrual blood provides a preparatory intraperitoneal dose of degenerating menstrual fluid. At succeeding menses the subsequent doses excite anaphylactic crises of colic, asthma, and rhinopathy.

⁵²⁰ GEBER, R. Arch. d. mal. de l'app. digestif 25: 972, 1936.

⁵²⁸ PHILLIPS, E. W. Southwest Med. 27: 144, 1943.

⁵²⁹ MALININ, A. J. Dermat. Wochenschr. 83: 1880, 1926.

lated papules and pustules, for which treatment is not really required, some cases present severe and extremely refractory lesions. During the past ten years, the writers have seen about 50 instances of acne in which a complete cure was achieved by means of injections of premenstrual serum (Figs. 35, 36)

A M., a 17-year-old white girl, presented an acne form eruption on the face, back, and chest. The lesions were said to have appeared for the first time three years previously, at the time of the menarche. They always flared four or five days premenstrually and receded about two days after the onset of the menses. Considerable dysmenorrhea was noted each month. Blood was drawn for serum and the patient received six injections of 0.2 cc. each in the first month

for ten or twelve years past. These lesions generally lasted from seven to ten days then gradually healed without leaving scars. The herpes appeared at the onset of each menstrual period. There was severe dysmenorrhea causing temporary but complete disability. The patient when first seen, had crusted localized vesicular patches with erythematous bases, on the left side of the mouth and on the cheek and right lower lip. Blood was withdrawn for the preparation of premenstrual serum. The patient received seven intradermal injections (0.2 cc. each) during the intermenstruum. No herpes appeared on the first day of her menses but during the last two days she developed a severe cold with typical herpes which was less severe than usual. However, menstrual cramps and pain did not appear and this, she said, was the first time in twelve years that she had been able to carry on her normal work without discomfort. The



FIG. 402 NEURODERMATITIS ON ENDOCRINE BASIS, FLARING TWO DAYS BEFORE EACH MENSTRUATION

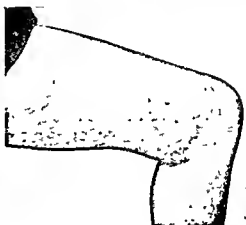


FIG. 403 DEFINITE IMPROVEMENT FROM ENDOCRINE THERAPY (ESTROGEN AND PROGESTERONE)

(without observable improvement) and eight injections the following month. At the time of the next menstruation, the patient presented only an occasional pustule and the condition of the skin was generally better. In the third month, she received nine injections and at this time was very much improved—the recession was estimated at 90 per cent. She also stated that her menstrual pain and discomfort had markedly decreased. No treatment was given the next month, and the face remained clear at the time of menstruation during the nine months the patient was kept under observation. Menstrual discomfort was still decidedly less than before.

Moreover, treatment with autogenous premenstrual serum has quite frequently been efficacious in curing generalized or localized (vulvar) pruritus, as well as herpetic eruptions usually located on the lips, face, or external genitalia.

J. S., 35 years old, white, had noticed grouped vesicular herpetic lesions on the lips and perioral folds

next month the patient received nine injections, and menstruation was delayed by eight days, although it had previously always been regular. The menses were not accompanied by herpetic vesicles or dysmenorrhea. The patient was perfectly well subjectively and objectively, for the next six months.

It may be noted that in a series of cases of pruritus vulvae and acne aggravated at the time of menstruation, Zondek and Bromberg³⁰⁸ obtained positive skin tests with steroid hormones in 72 per cent.

Urticaria, angioneurotic edema, neurodermatitis (Figs. 402, 403), localized and generalized menstrual dermatitis (Figs. 404, 405, 406), including the so-called dermatitis dysmenorrhoeica (Figs. 407, 408), appear far less commonly in conjunction with menstruation. The last-mentioned term goes back to the days when it was first discovered that the obvious connection between this dermatosis

and menstrual irregularity could be convincingly demonstrated. The question as to whether the condition is an expression of a menstrual toxicosis or a menstrual allergy

especially at the time of menstruation this may surely be interpreted as a definite indication that the following conditions are the expression of an endogenous hormonal allergy

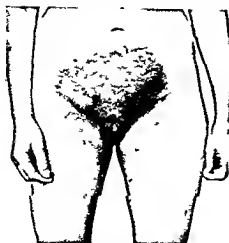


FIG 404 PERIVULVAR DERMATITIS OCCURRING PREMENSTRUALLY

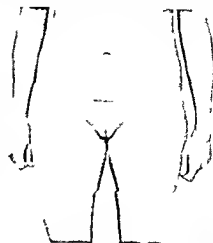


FIG 405 CURE BY ESTROGENIC THERAPY

must often remain unanswered even today. The writers have shown that such dermatoses can be successfully treated by appropriate endocrine therapy. Another approach is to persuade the patient to become pregnant. In cases resistant to other forms of therapy, X ray castration may be employed as a last resort.

It is occasionally possible to demonstrate that in dermatitis dysmenorrhoeica (FIGS 409-410) the premenstrual blood contains a substance that when injected into the skin of the patient in the intermenstruum will evoke an immediate urticarial reaction (FIG 411) and a delayed response in the form of pinpoint sized papules clinically resembling the lesions of the menstrual dermatosis. However, the patient does not react to her own blood serum withdrawn in the intermenstruum or to the premenstrual serum of normal individuals. In controls on the other hand it is impossible to elicit either an immediate or a delayed reaction by injecting premenstrual blood serum from the patient.

Moreover, considerable improvement and often complete cure can be achieved by administering premenstrual serum not only in the dermatoses but also in all the other conditions appearing either exclusively or prin-



FIG 406 GENERALIZED MENSTRUAL DERMATITIS OF SIXTEEN YEARS DURATION FINALLY CONTROLLED BY ENDOCRINE THERAPY

menstrual migraine (Cameron⁵²³, Urbach and Gottheb⁵²⁴), menstrual trigeminal neuralgia (Geber⁵²⁵), menstrual asthma (Salem⁵²⁶, Urbach), menstrual rhinopathy (Urbach), certain cases of premenstrual tension (Urbach). In a

diabetic girl recently observed by the senior author, the regular occurrence of vomiting and abdominal cramps one day before men-

Less commonly, still other conditions are associated with menstruation and the possibility of an endogenous-allergic mechanism.

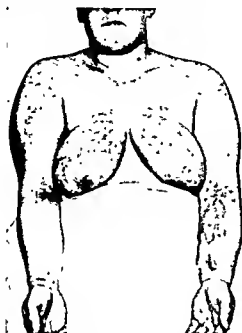


FIG 407 GENERALIZED MENSTRUAL DERMATITIS (DERMATITIS DYSMENORRHOICA)

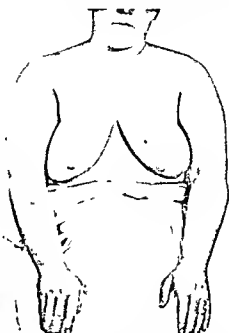


FIG 408 RESULT OF X-RAY CASTRATION, RESORTED TO AFTER FIFTEEN MONTHS' HOSPITALIZATION DURING WHICH ALL FEASIBLE TREATMENTS WERE TRIED

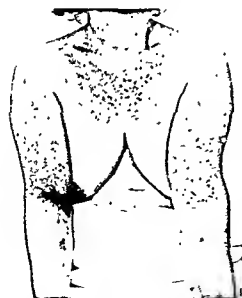


FIG 409 PREMENSTRUAL EXACERBATION OF DERMATITIS DYSMENORRHOICA



FIG 410 SAME PATIENT BETWEEN MENSTRUATIONS

struation repeatedly threatened to precipitate diabetic coma. Autoserotherapy completely prevented the vomiting and cramps.

Menstrually recurring purpura of the Schoenlein-Henoch type was thought by Ellman and Weber²⁹⁰ to be of anaphylactic origin.

Minot¹⁰ noted blood eosinophilia in two cases of menstrual thrombocytopenic purpura and suggested a possible allergic background. Rarely jaundice accompanies each menstrual period in certain individuals (Lichtman⁷¹). This may be due to edema or spasm (dyskinesia) of the sphincter of Oddi or possibly to a functional disturbance of the liver parenchyma. It is reported that the benzotic acid test of liver function is diminished during the first day of menstruation (Heilg and Kantien⁷²).



FIG 411. ISOMORPHIC DERMATOUS REACTION (M) TO PATIENT'S OWN PREMENSTRUAL SERUM INJECTED INTRACUTANEOUSLY DURING INTERMENSTRUUM.

Note negative controls with patient's own serum withdrawn in intermenstruum (N) and with premenstrual serum of normal woman (C).

In connection with skin diseases related to endocrine function it might be pertinent to mention that the senior author has observed a few cases of dermatitis, acne, and pruritus that showed distinct exacerbation at the time of the rupture of the graafian follicle and that could be controlled by appropriate hormonal therapy. According to Godel⁷³ allergic manifestations in general are exaggerated during

ovulation as well as during menstruation and the menopause.

Isolated observations (Rowe⁷⁴, Smith⁷⁵) suggest the possibility of a relationship between painful menstruation or excessive menstrual flow and hypersensitiveness to some food. This does not, however, permit the assumption that all cases of essential dysmenorrhea are of allergic origin—a view that certain authors are now inclined to take. Joachimovitz⁷⁶ reported a case in which the allergic menorrhagia was aggravated by topical application of the allergen to the cervix, and the menstrual fluid contained large numbers of eosinophils. Labor-like pains and sudden onset of bleeding outside of the menstrual period have repeatedly been observed (Duke⁶⁰, Kahn⁷⁷, Smith⁷⁸) as part of a severe generalized allergic reaction—e.g., following injection of an overdose of antigen. Hansen⁷⁹ reported an abortion following a generalized reaction to an injection of pollen.

Furthermore, an occasional case of leucorrhea, especially when marked by an abundance of eosinophilic cells, may also be attributable to allergy. Adelsberger and Munter¹⁶⁹ reported instances of this kind during the hay fever season in women suffering from pollinosis. In a similar case Thomas and Wicksten⁹⁸ found that the application of a small amount of ragweed pollen to the posterior wall of the vagina produced a definite reaction characterized by increased redness and puckering of the mucous membrane locally, along with an increase in watery discharge from the cervix. Another case of leucorrhea in a patient with allergic rhinopathy showed a large number of eosinophils in the vaginal secretion. The leucorrhea was controlled by elimination of certain foods, especially eggs and wheat, and hyposensitization with respect to the inhalant factors. The senior author has observed an instance of specifically caused vaginal discharge found to be a partial expression of a food allergy (pork) as confirmed by appropriate elimination and reexposure experiments. H. L. Huber traced pruritus vulvae appearing in 3 children during the ragweed

¹⁰ MINOT G. R. *Am J M S* 1924; 1936.

⁷¹ LICHTMAN S. S. Diseases of the Liver. Griffling and B. L. Du S. Philadelphia, Lea 1912; p. 613.

⁷² HEILG R. and KANTHENG N. L. *Ann Int Med* 16: 538, 1942.

⁷³ GODEL R. *Prescribed* 48: 95, 1940.

⁷⁴ ROWE A. H. *Am J Obst & Gynec* 24: 333, 1932.

⁷⁵ SMITH D. R. *J M Socour N A* 28: 342, 1931.

⁷⁶ JOACHIMOVITZ I. S. *J A M A* 90: 201, 1938.

pollinating season, to local contact with pollen.

Finally, the altered reactivity of the skin at the time of menstruation should be considered briefly. Clinical experience indicates that a state of cutaneous hypersensitiveness is frequently present in the premenstrual period and during the first days of menstruation. Certain discordant observations should, however, be mentioned. Thus, Hansen-Pruess and Raymond²⁷⁷ maintain that in allergic women the strongest average reaction to allergens is obtained on the last day of menstruation; the next greatest in the midperiod of the cycle; and the smallest on the premenstrual day. In other words, the increase in skin reactivity seems to be associated with periods of low estrogenic titer in the blood. The same fact was demonstrated by Coulaud²⁷⁸ with regard to the tuberculin reaction in women. However, since the results of these studies contradict clinical experience, further investigation seems to be warranted. The varying degrees of hydremia and dehydration may possibly play an important rôle in determining the degree of the skin reaction during the menstrual cycle, since it is a well-known fact that there is a state of relative hydremia in the premenstrual period and a state of relative dehydration on the last day of menstruation.

B. PREGNANCY

The effect of pregnancy on pre-existing allergic states is not uniform. However, aside from those conditions appearing in certain patients only when they are gravid and probably dependent on an endogenous allergy, it may be stated as a broad generalization with many exceptions that the manifestations of hypersensitiveness often tend to be milder or even absent during pregnancy. Zondek and Bromberg²⁷⁹ suggest that in view of the probability of endogenous allergy to normal hormones, the frequently observed improvement in allergic diseases at this time may be explained by the assumption that the gradual increase of the hormonal level of the body during pregnancy brings about hormonal desensitization. Another possibility is sug-

gested by Ahlmark's²⁷⁷⁹ observation that elevated histaminase activity of the blood in human beings may be detected during the seventh week of pregnancy and increases in the second half of pregnancy to 500 to 1,000 times above normal. The same findings were noted in guinea pigs and rats, although not in cats and rabbits. However, on the basis of the reactions to tuberculin in pregnant tuberculous women, Lichtenstein²⁸⁰ objects to the concept of "anergy of gravids," although he did note a mild diminution of sensitivity during the third trimester of pregnancy in 25 per cent of the patients. A return to normal reactivity occurred shortly after delivery.

What we call a pregnant organism is a unique biologic system, consisting not, as long believed, of two components, but of three: the mother, the placenta, and the fetus. It should be pointed out that there is no direct, immediate relation between mother and fetus, while the most intimate physiologic relationship exists between the placenta and the mother's organism, on the one hand, and between the placenta and the fetus, on the other.

With these reservations established, it may now be pointed out that during pregnancy there is an exchange between mother and fetus of certain substances that are always foreign—and therefore antigenic—to one of the two. According to Naegeli's²⁸¹ brilliantly conceived hypothesis, it may be said that, in the normal course of pregnancy, there is a very gradual and slowly increasing passage of the antigens, making possible a reciprocal saturation of the antigens and antibodies. As a result, the organism of the mother and probably also that of the fetus become so perfectly attuned that they produce a state of specific anergy. Nevertheless, even in pregnancies running a perfectly normal course, temporary disturbances (nausea, vomiting, and the like) occur often enough, both at the beginning and toward the end of the pregnancy; they may possibly be interpreted as symptoms of specific endogenous hypersensitiveness. The question of the transmission of antigens and antibodies through both the normal and the patho-

²⁷⁷ HANSEN-PRUESS, O. C., and RAYMOND, R. J. Clin. Endocrin. 2, 161, 1942

²⁷⁸ COULAUD, E. Médecine 4, 627, 1923

²⁷⁷⁹ AHLMARK, A. Lancet 2: 406, 1944

²⁸⁰ LICHTENSTEIN, M. R. Am. Rev. Tuberc. 66: 89, 1942

²⁸¹ NAEGLI, O. Muenchen med. Wchnschr. 76: 787, 1929.

logic placenta assumes great importance in the problem of allergization of the fetus in utero (p 48) and of the passive Rh isosensitization of the newborn, resulting in erythroblastosis fetalis (p 366), and is further considered with these subjects

It has long been known that placental protein is origin to the gravid organism this point is supported by the facts that the serum of a pregnant woman possesses the capacity of breaking down placental protein, and that, following injections of placental protein, the blood of the pregnant woman demonstrably contains specific antibodies to it. The existence of anti-placenta antibodies was experimentally demonstrated by Seegal and Loeb⁵¹⁸ and injection of anti placenta serum into pregnant rats was found to lead to fetal death by degeneration of the placenta. Moreover, as Gans⁵²² has shown in an extensive series of experiments, while intracutaneous injections of various organ extracts elicit definitely weaker reactions in pregnant women than in nonpregnant women or in men, this situation is reversed when pregnancy serum is added to the extracts in other words, injections in pregnant women of organ extract plus pregnancy serum evoke local reactions that, with regard to intensity and persistence of the erythema and infiltration, definitely exceed those elicited in nonpregnant women and in men. This would seem to warrant the conclusion that pregnancy serum contains a substance to which the pregnant organism is hypersensitive, the substance may well be an endogenous hapten (see p 120), since pregnancy serum alone is incapable of eliciting these reactions

Proceeding from the working hypothesis that the fetus represents an antigen to which the gravid organism responds with antibody formation, the senior author⁵¹⁷ gave pregnant women intracutaneous injections of 0.1 cc of fetus extract. For this purpose, fetuses approximately 6 to 8 weeks old, surgically removed because of ectopic pregnancies, were crushed in a Buchner press under aseptic conditions, the filtrate was diluted with physiologic saline solution and passed through a Berkefeld filter. It was found that nonpreg-

nant women and those in the early months of pregnancy responded with strongly positive skin reactions after twenty four hours, while women in the last trimester of pregnancy presented either no response at all or only a very mild reaction. The results of these experiments strongly suggest that the pregnant organism in time acquires a specific anergy to fetal protein

The assumed presence of specific antibodies in the pregnant woman serves to explain the good results achieved with systematic injections of the serum of pregnant women in the treatment of the dermatoses of pregnancy (Freund⁵²³) the administration of these antibodies effectively neutralizes the increased supply of antigen in these diseases

The conditions that will be discussed below under the general head of allergic diseases of pregnancy were and are even now often called "pregnancy toxicoes." Yet the outstanding men in this field admit that, despite all efforts, it has never been possible to isolate any definite protein derivative from the blood or urine of the pregnant woman, or to demonstrate conclusively the presence of any kind of toxin. However, according to Seitz, the disease pictures so closely resembling a toxicoes are produced not by toxins in the strict sense of the word, but by physicochemical alterations of the blood or tissues. This concept is extraordinarily close to that expressed by Doerr and other authors with reference to the pathogenesis of allergy (see p 37)

The symptomatology of the allergic diseases of pregnancy comprises subjective and objective manifestations, the latter being divided, in turn into local cutaneous and general internal disturbances. One of the most distressing symptoms is pruritus, which sometimes appears at the beginning of pregnancy, sometimes only in the later months, and is often extremely severe. In other cases, there is lichen urticatus (Fig 412), and erythemas and urticarial exanthems have occasionally been observed. The beneficial effect of therapy with the serum of normal pregnant women has been mentioned above as evidence regarding the allergic nature of these conditions

Nasal symptoms constitute another syn-

⁵²² GANS, O. *Dermat. Wochenschr.* 73: 841 1927.

⁵²³ FREUND, N. *Berl. klin. Wochenschr.* 46: 652 1909

drome sometimes occurring in pregnancy. Thus Mohun¹⁸³¹ observed 8 patients who experienced a severe degree of nasal blocking and congestion only during pregnancy, and 5 of them reported similar symptoms during one or more previous pregnancies. Typically, the condition disappears spontaneously within one to seven days after delivery. He concluded that the increased incidence of rhinopathy during pregnancy appeared to be parallel to and caused by the amount of estrogen produced in the body.

semen was proved by a definite time relationship between the symptoms and the deposition of semen in the patient's vagina (mild nausea for three days followed by sudden onset of vomiting for five days) and by positive passive transfer tests with the semen.

The disturbances generally included under the term eclampsia are more dangerous and therefore far more important. The pathologic picture of eclampsia is a sharply circumscribed one, particularly as regards the renal and hepatic involvement. The kidney presents a



FIG 412 ENDOGENOUS ALLERGY TO FETAL PROTEIN

Lichen urticatus in pregnant woman from sixth to ninth month. Skin cleared completely two days after delivery.

Nausea and vomiting of early pregnancy may be due to an allergic reaction of the patient to the secretion of her own gravid corpus luteum (Finch³⁴⁸). Intradermal injection of luteal hormone in such patients produced a typical allergic wheal, while no reaction was elicited in pregnant women not suffering from nausea. He claimed that the symptoms can be alleviated and even completely controlled by injections of graduated doses of progestin. A unique and interesting mechanism appeared to account for pernicious vomiting of pregnancy in a case studied by James and Wagoner²²³⁴: sensitivity to the husband's

picture suggestive in part of an unusual type of nephrosis, along with involvement of the glomerular capillaries. Less constantly the liver reveals changes in the periphery of the lobules, consisting of fibrinous thrombi in the portal vessels and hemorrhages, furthermore, there is cell destruction in the involved parts. In this connection it is interesting to note that, while engaged in experimentally producing allergic acute diffuse glomerulonephritis, Ahlstrom²²³⁵ observed hepatic changes that morphologically corresponded in many respects to those seen in the livers of individuals suffering from eclampsia.

A number of theories have been advanced to explain eclampsia, including postulation of a

²²³⁴ JAMES, D. W., and WAGONER, C. P. Letters, Internat. Cong. Club. of Allergy, Series 7: 70, 1944.

toxic state due to substances coming from the fetus of increased production of posterior pituitary hormone, of disturbances in the endocrine glands of cerebral edema, and of increased intracranial pressure as a result of changes in the kidneys. None of these can explain all the symptoms of eclampsia. On the other hand, if the facts are evaluated objectively, a certain modicum of truth will have to be granted to each possibility. How can these ideas be reconciled? The answer would seem to lie in abandoning the search for the cause of eclampsia among morbid states of the individual organs (placenta, kidney, liver, pituitary, brain), or in faulty chemical regulation, as acidosis and in accounting for the various clinical and pathologic manifestations on the basis of an altered reaction capacity to the fetus on the part of the gravid organism.

Investigations to support the view that eclampsia is an expression of hypersensitivity of the maternal organism to placental protein go back to the experimental studies of Rosenau and Anderson.^{32,35} These authors showed that guinea pigs can be allergized to extracts of guinea pig placenta. However, this demonstration was considered inconclusive, since the characteristic pathology of puerperal eclampsia was never reproduced in experimental anaphylaxis. However, Yamada³⁴ recently found that eclamptic changes of the spleen, liver, kidneys, and adrenals can be induced in pregnant rabbits by repeated intravenous injections of placental proteins from an eclamptic patient. This investigator also showed that when the isolated uterine musculature of guinea pigs is sensitized to eclamptic human serum, it is thrown into acute anaphylactic tetany by addition of eclamptic placental proteins to the solution in which the uterus is suspended. On the basis of these experiments, Yamada concluded that an abnormal and highly antigenic protein is given off by the eclamptic placenta, and that this substance reacts with homologous maternal antibodies in such a way as to account for the entire syndrome.

The assumption that this disease is of allergic origin receives further support from the

investigations of Knepper^{32,36} who apparently succeeded in reproducing the pathologic picture of eclampsia in animals by inducing serum anaphylaxis along with simultaneous injections of the posterior pituitary hormone.

Furthermore Junghans^{37,37} furnished support of the theory of the allergic causation of eclampsia by demonstrating that women with pre eclampsia give strongly positive skin reactions to intracutaneous tests with fetus extract while no such reactions are given by healthy pregnant women.

On the basis of these findings Junghans^{37,37} and other authors assume that the clinical manifestations associated with eclampsia including the headaches, convulsions and temporary loss of vision and of consciousness are attributable to an allergy—all the more so since these manifestations are known to occur in the symptomatology of allergic diseases. It may be assumed however that certain as yet unknown factors must be present in order to promote such a high degree of sensitization of the maternal organism to fetal protein.

Some authors actually claim that the very mechanism of birth (onset of labor, expulsion of the fetus) is also brought on by allergic processes. These claims are utterly without foundation. Moreover it must be said that idle speculation of this kind can only bring harm and discredit to the study of allergy.

Therapeutically the treatment of the allergic conditions of pregnancy is still confined to systematic intramuscular administration of normal pregnancy serum (10 cc twice weekly for about five or six injections) and to a methodical modification of the diet with the purpose of reducing the intake of animal protein to a minimum. In severe cases of eclampsia, the physician will have to consider the advisability of interrupting the pregnancy.

C MENOPAUSE

The influence of the menopause is rather difficult to evaluate. Unlike the situation in menstruation and pregnancy, there are no specific allergic diseases that are exclusively or chiefly dependent on the menopause. In

^{32,35} ROSENAU M J and ANDERSON J F *Hyg Lab Bull* 45
U S Pub Health Service 1938

³⁶ KNEPPER R Kln Wchnschr 13 1751 1934

^{37,37} JUNGHANS E Arch f Gynak 168 656 1939

some instances, the cessation of ovarian activity is unquestionably very beneficial. This is particularly true in relation to migraine—a common observation that has even led to artificial interruption of ovarian function in intractable cases. Furthermore, asthma is sometimes favorably influenced by the menopause. On the other hand, there are many patients in whom the heightened irritability

and nervous tension of this age are responsible—probably because of autonomic or central nervous system imbalance, or of endocrine factors—for the aggravation of and sometimes even the onset of allergic diseases, including urticaria, dermatitis, rhinopathy, and asthma. To ascertain or rule out a pathogenetic relationship, estrogenic therapy may be tried, and will bring prompt relief in appropriate cases.

ALLERGY IN THE NEWBORN, IN INFANCY, AND IN CHILDHOOD

IN THE last years of his life, von Pirquet subscribed to the view that there is such a thing as a special allergy of childhood, of maturity, and of old age, respectively. However, this view may now be categorically rejected. Although it is true that particularly in childhood certain allergic manifestations appear that are never observed in other age groups (such as special allergic conditions of the newborn, or infantile dermatitis), the underlying allergic mechanism is always the same. However, in order to offer a concise summary of the conditions in question, we shall either here review the allergic diseases appearing in childhood, or refer to the chapters in which a more detailed discussion of each subject is available.

A CLINICAL MANIFESTATIONS IN THE NEWBORN

Some of the manifestations to be described below have been grouped by Mayerhofer²²³ under the term "biologic allergy of infancy." As he pointed out, there occurs during the last months of pregnancy an uninterrupted transmission, from mother to fetus, of various protein substances that are foreign to the latter such as the maternal sex hormones or placental proteins. All these substances are capable of allergizing the infant's organism *in utero*, in general however, no definite allergic reaction can take place so long as the placenta exerts its "detoxifying" action. It is only after birth * when this mechanism is no longer available, that the remaining traces of maternal protein can evoke allergic reactions in the newborn.

This concept would make it readily comprehensible that many of the conditions and processes of early infancy considered by Mayerhofer to be of allergic origin, are actually

to be regarded not as pathologic or morbid but as strictly biologic phenomena. To what extent they will in the future be recognized as allergic or pathergic, will depend on whether or not it will be possible to demonstrate the presence of an antigen-antibody mechanism. Mayerhofer attributes such great importance to these conditions that he draws the line of age distinction between the newborn and infants on the basis of their individual capacity to present the allergic reactions typical of the newborn. He considers the age of 42 days to be the maximum limit of the newborn stage.

Mayerhofer recognizes the following clinical pictures of allergy of the newborn:

(1) *Erythema toxicum neonatorum* (Leiner-Moussons) *allergic exanthem of the newborn* (Mayerhofer). Approximately 50 per cent of all newborn infants present a skin eruption that is similar either to measles or to the skin manifestations of serum exanthem. These infants not uncommonly have the following additional symptoms that may also be of allergic origin: initial leucopenia, relative and absolute eosinophilia of the blood at the peak of the exanthem, splenomegaly, lymphadenopathy, and recurrences of the rash as in "fractionated" serum exanthem. Rosenbaum, Sokolow and Kononova, Pehu and Wöringer, Peipers, and other pediatricians have accepted Mayerhofer's view that *erythema toxicum neonatorum* is of allergic origin (for bibliography see Mayerhofer²²⁴).

(2) *Pylorospasm of the newborn*. Between the seventh and fourteenth days of life many nursing infants suddenly begin to vomit spasmodically. Mayerhofer interprets this symptom as an allergic reaction to the mother's milk. The condition is not a serious one, and clears up spontaneously.

(3) *Melena neonatorum*. This condition may, naturally, be of pathologic origin (erosions or necrosis of the gastro-intestinal mucosa, or other organic lesions). However, in many instances, it runs its course without any apparent pathologic cause. It almost invariably appears on the seventh day of life

²²³ MAYERHOFER, E. *Wien med. Wochenschr.* 85: 57, 1935.

* An apparent exception to this statement is found in the observation of McGee²²⁵ of 21 cases of fetal hiccups observed by him. It was possible in 5 to give the mother a particular food and at a will to produce the hiccups in the unborn child. These children later were highly allergic.

²²⁴ MCGEE, A. *Discussion to Ratner* 1933.

Mayerhofer considers this form of melena to represent an allergic intestinal reaction; in his opinion, it requires no treatment.

There is, however, as pointed out by Rubin,³²⁹⁰ another type of melena in newborn infants, which is due to hypersensitiveness to cow's milk. It can be controlled in some cases by substituting milk from another animal species, or sometimes only by a milk-free diet.

(4) *So-called dyspepsia of the newborn.* Following complete elimination of meconium, watery mucoid greenish stools are very commonly observed. The older school of pediatricians generally called these "dyspeptic stools." Mayerhofer, however, considers this intestinal catarrh to be of allergic origin. The correct pathogenetic evaluation of these intestinal manifestations is of therapeutic significance, since these catarrhs should not be treated with starvation and laxatives; conservatism usually suffices, since the symptoms generally retrogress spontaneously.

(5) *Allergic hydrocele in the newborn.* Many but not all hydroceles in the newborn appear during the seventh to tenth days of life, their onset being extraordinarily abrupt and sometimes involving very stormy manifestations. Mayerhofer regards the mechanism of this exudation in the still unclosed space of the tunica vaginalis propria as analogous to the allergic joint exudation in serum sickness; for this reason paracentesis should not be performed. His assumption seems to find support in the findings reported by Papp and Steinert,³²⁹¹ that puncture of the hydrocele disclosed long pointed needle-like crystals, assumed by the authors to be Charcot-Leyden crystals.

(6) *Fetal erythroblastosis.* The syndromes of congenital hemolytic anemia or icterus gravis neonatorum are today considered to be an expression of isoimmunization, or better, isosensitization in the pregnant mother (Levine, Katzin, and Burnham³²⁹²). The isosensitization is probably due to the fact that an Rh-positive fetus produces anti-Rh iso-antibodies in an Rh-negative mother; if these antibodies filter back into the fetal circulation,

they have a destructive effect on the blood of the fetus, the expression of which is the condition of icterus gravis. As a proof of their theory, Levine et al.³³⁰¹ demonstrated that while only 15 per cent of persons taken at random are Rh-negative, 90 per cent of the mothers of erythroblastotic infants were found to be Rh-negative. Moreover, the serums of many of these mothers were found to contain anti-Rh agglutinins. Fetal erythroblastosis and its mechanism are discussed at greater length in chapter XV.

According to the answers obtained from a questionnaire sent to several hundred obstetricians, allergists, and pediatricians and to his own experience, Campbell³⁷¹³ states that the following suggest the possibility of potential allergy in the newborn, although he fails to delimit the duration of the neonatal period:

- History of allergic parentage
- Unstable parentage
- Retroauricular intertrigo
- Seborrhea capitis, with or without involvement of the shoulders, arms, eyebrows, elbows, and popliteal spaces
- Loose stools, mucoid stools, or intestinal bleeding after ingestion of cow's milk
- "Geographic tongue"
- Visible peristaltic waves
- Intrauterine hiccup
- Nose rubbing or sneezing (with eosinophils in nasal smears)
- Continuance of vomiting after pyloromyotomy in infants with pyloric stenosis
- Excessive hunger on adequate formula (probably abdominal discomfort or colic)
- Allergic colic (to be differentiated from colic due to acrophagia)
- Excessive reaction to silver nitrate drops, or to ammoniated mercury or other agents used to prevent impetigo
- Urticaria immediately after breast feeding, usually disappearing before next nursing (probably due to allergen in mother's diet, such as chocolate, rhubarb, asparagus, rather than to specific reaction to human milk protein)
- Intolerance to orange juice or cod liver oil
- Unusual sensitivity to sugar
- Early excretion of the buttocks
- Asthma (especially if nursing mother's scalp shows excessive dandruff)
- Laryngospasm
- Glossitis (rare)
- Edema of hands and feet
- Enlargement of thymus

³²⁹⁰ RUBIN, M. I. *Pennsylvania M J* 45: 711, 1942

³²⁹¹ PAPP, G., and STEINERT, G. *Ztschr f Kinderh* 55: 726, 1943.

³²⁹² LEVINE, P., KATZIN, E. M., and BURNHAM, L. *J A M A* 116: 825, 1941

While it is impossible to agree to the significance of all these manifestations, the length and variety of the list indicate the protean possibilities of neonatal allergy and explain why it is so often unsuspected.

Of 200 allergic children seen by Campbell, 25 per cent revealed signs of allergy soon after birth, in comparison, Clein²⁴⁹ reported that the first allergic symptoms appeared in 39 per cent of 100 allergic children in the first month of life, and 24, 13, and 6 per cent, respectively, in the ensuing months.

The possibility of anaphylaxis caused by human breast milk is illustrated by two cases described by Campbell⁷¹³

A newborn infant whose older brother had died of anaphylactic shock after his first breast feeding presented similar symptoms when one drop of his mother's milk was placed on his tongue. He was promptly weaned. One month later he gave a strongly positive reaction to human breast milk.

Another infant on being placed to the breast on the second day of life went into a state of anaphylactic shock so severe that the head nurse baptized him during the episode. He was resuscitated by epinephrine and artificial respiration. The same thing occurred the following day when he was given one drop of his mother's milk. He was proved allergic to human milk by skin testing.

B. CLINICAL MANIFESTATIONS IN INFANTS AND CHILDREN

The relative frequency of involvement of the various systems depends, to a great extent, on the age of the child. The infant will most commonly present gastro-intestinal symptoms due to food allergy, as well as cutaneous manifestations, the causes of which may vary considerably from case to case. While asthma sometimes does occur very early in life, it is rarely encountered in children under the age of 2 years. Rhinopathy, including hay fever, generally makes its initial appearance even later, mostly at the age of 4 or 5 years.

A survey of 1,000 children, undertaken by Rudolph,⁷⁹³ revealed allergic manifestations in infants as young as 4 months. In order of frequency, these were dermatitis, gastro-intestinal symptoms (frequent vomiting, severe colic, diarrhea, constipation), sneezing, urti-

caria, and wheezing. Hill⁷⁹⁴ quite properly states "The allergic child is never static, his allergic pattern is continuously changing, he is becoming acclimated to some allergens and sensitized to others."

It might also be said, on the basis of Clein's²⁴⁹ observations, that the nature of the allergic manifestations is equally subject to change. In 100 cases the initial allergic symptoms in the order of frequency were rash or dermatitis, usually due to egg yolk or orange juice, vomiting or pylorospasm, other gastro-intestinal allergy, manifested by severe persistent colic, flatulence, recurrent diarrhea, or constipation, and far less frequently, asthma, perennial rhinopathy, "allergic tongue," hay fever, and urticaria. Despite early diagnosis and prophylactic treatment, 98 per cent of these developed major allergic diseases within a ten year period of observation—85 per cent of them before the age of 7 years. These included, in order of frequency, perennial allergic rhinopathy, hay fever, bronchial asthma, dermatitis, gastro-intestinal allergy, and urticaria, as well as other diseases. About half of the series had only one diagnosis, the remainder two or more. Significantly, the nature of the first allergic symptom did not usually determine the type of allergy developing subsequently, although those with pyloro-spasm in infancy tended to exhibit gastro-intestinal allergy or urticaria later, while those with gastro-intestinal conditions in infancy had less chance of dermatitis.

Ballester²⁴¹ points out that impaired nutrition is present to a variable degree in all allergics, especially in children, and may outweigh the other allergic symptoms in importance, or even be the only manifestation. Allergic children may be as much as 50 per cent underweight, and about one third are 15 per cent or more underweight. Characteristically, the fat loss is greater in the thoracic region than in the abdomen.

It is easy to understand that the principal allergens in infancy and early childhood are foods. Inhalants become about equally important in the latter part of the preschool age period, and the incidence of sensitivity to inhalants (dust, feathers, pollens) and bacteria increases throughout the school years. Drugs play a relatively minor rôle, although there

have been increasingly frequent reports of sensitization to the sulfonamides in children.

The literature contains many studies on the subject of personality trends in allergic children. Representative of these is the work of Riess and de Cillis,²⁷⁴ who submitted 139 allergic and 117 nonallergic youngsters to various psychologic tests. The former were, as a rule, found to be more ascendant, extroverted, and emotionally unstable than the latter. Children with skin allergies exhibited this type of psychic make-up more than did those with rhinopathy or asthma. Stokes²⁷⁵ described the neurodermatitic child as ceaselessly active, precocious, assertive, and egocentric. Hurst²⁷⁶ and Rogerson²⁷⁷ found the asthmatic child to be above the average in intelligence, irritable, aggressive, dominating, quick to respond, overanxious and overcautious, insecure, and lacking confidence in himself. In nearly all allergic children, marked nervousness is a prominent symptom. In a strikingly high proportion of cases, the child occupies a position in the family that seems to subject him to unusual psychologic strain. He is the special object of the family's anxiety and care (Rogerson²⁷⁸). Appropriate psychotherapy, directed as much toward adults in the environment as to the patient himself, may prevent attacks. Moreover, as Friedjung²⁷⁹ most emphatically stresses, the physician must always take into account the possibility of other psychologic influences. Thus, the child's position in the order of age, or in the distribution of the siblings with regard to sex, must receive consideration, since such factors may make him feel remote from his parents or from his brothers and sisters. Similar difficulties also arise at kindergarten or at school, of course, as the result of the attitude of the child's teacher or classmates. Lastly, the physician will have to pay special attention, in some cases, to compulsion neuroses and fear manifestations.

Finally, parents should not be assured that their child will "outgrow" an allergic disease. Although this sometimes does happen, it is the exception rather than the rule. Moreover, many of those in whom this apparently takes

place will be found, if observed for a sufficient length of time, to present the same or other allergic manifestations later. Black²⁸⁰ estimates that not more than 10 per cent of allergic children recover spontaneously—certainly a small enough proportion not to warrant neglect of etiologic diagnosis and appropriate treatment.

1. RESPIRATORY TRACT

RHINOPATHY

The fact is not as yet sufficiently appreciated that conditions classified under the general heading of infections of the upper respiratory tract, or sinusitis, are often manifestations of allergy in children. We refer most particularly to the recurring head colds characterized by a "stuffy nose" that is at its worst on arising and gradually improves and even completely clears up after several hours, and by a nocturnal hacking dry cough, without demonstrable physical findings. When such conditions are not infectious, they are suggestive of an allergic etiology. These little patients recover from one such "cold" only to suffer another. The condition begins and ends abruptly, and lasts from several hours to several days. Nasal congestion and obstruction, sometimes sneezing spells, and almost invariably itching of the nose, are the most apparent clinical symptoms. The last-mentioned is a particularly important and characteristic sign. A child suffering from an allergic nasal condition will, as a rule, rub his nose vertically by pushing his palm upward against the tip of his nose, a gesture that Vaughan²⁸¹ calls the "allergic salute"; in the case of a true infectious cold, on the other hand, the child will usually rub his nose from side to side. The purpose of the former gesture is both to relieve the itching and to spread the nasal walls, so securing better nasal ventilation. Frequent "sniffing" and nose-wrinkling are other suggestive mannerisms.

The differentiation of an allergic rhinopathy from an infectious rhinitis is of paramount importance from the therapeutic viewpoint, for institution of proper treatment may prevent the development of asthma when the child grows up. Moreover, as has been pointed out by Peshkin and others, children

²⁷⁴ RIESS, B. F., and CILLIS, O. E. *DE J. Abnorm. & Social Psychol.* 35: 104, 1940.

²⁷⁵ ROGERS, C. H. *Brit. J. Dermat.* 46: 358, 1954.

²⁸⁰ BLACK, J. H. *Texas State J. M.* 41: 21, 1945.

are less susceptible to acute colds and bronchitis when the allergic condition is controlled. The present writers have frequently made the same observation.

Table 64 modified from that of Cohen and Rudolph,²²⁹⁷ presents the differential diagnosis of the two conditions. The only objection

Finally, it must be borne in mind that many truly infectious nasal conditions are complicated by an underlying allergy and cannot, therefore, be cleared up until the specific hypersensitiveness predisposing the mucous membranes to infection is cured. These combined allergic and infectious cases are fre-

TABLE 64—*Differential Diagnosis of Allergic and Infectious Diseases of the Upper Respiratory Tract in Children*

D i a g n o s t i c F a c t o r	A l l e r g i c D i s e a s e s	I n f e c t i o u s D i s e a s e s
H I S T O R Y		
Attacks	usually recurrent	usually single
Persistence	often mild symptoms between attacks	usually complete clearing up
Relation to heredity	definite	none
Contagiousness	none	marked
Relation to exposure to another case	none	definite
Relation to foods and inhaled substances as cause	often traceable	none
Nasal itching	common	none
Wheezing	common	none
Other allergic conditions current or in history	usually present	usually none
P H Y S I C A L E X A M I N A T I O N		
Fever	only occasionally present, rarely high	usually present often high
Visible mucous membranes	pale glistening edematous	hyperemic red
Nasal discharge	thin watery or mucoid	mucopurulent or purulent
Sputum	mucoid	mucopurulent or purulent
Smear finding	numerous eosinophils	polymorphonuclear neutrophils predominant eosinophils few or absent
Blood count	frequent eosinophilia	often leucocytosis
Other signs of allergy	often present	none
Sinus involvement	edematous type	purulent type
Wheezing breath sounds	present	none
X ray finding	increased bronchial markings	no increase of bronchial markings
T H E R A P E U T I C R E S P O N S E		
Response to epinephrine	rapid and marked	none or slight
avoidance	avoidance of specific allergens followed by relief	avoidance of food or inhalant substances followed by no change

that might be raised concerns the statement that infectious rhinitis is not followed by wheezing breath sounds. In the not altogether infrequent cases of bronchitis asthma in children, nearly every attack of acute rhinitis is soon followed by wheezing

quently difficult to diagnose, especially in the acute stage. Repeated periods of close observation, with determination of the cytology of the secretions may be necessary before the allergic factor can be definitely evaluated. As a result of nasal congestion during the night, there is mouth breathing, snoring, and heavy respiration. Moreover, prolonged nasal

obstruction will in time lead to underdevelopment of the sinuses and retardation of vertical growth of the face and of its forward projection. This, according to Todd,³²⁹ produces a narrow, pinched nose and constriction of the upper dental or palatal arch, so that there is inadequate space for accommodation of the developing and erupting teeth. Failure of the sinuses to develop properly, as well as improper bony development, interferes with the facial growth, leading particularly to a depression of the bony prominence of the cheeks which assume a flat appearance, and produces the characteristic features of the so-called allergic facies. The rôle of allergy in the etiology of orthodontic deformities, including protrusion of the teeth and malocclusion due to poor bony growth, was stressed by Cohen,³²⁹ Bowen,³³⁰ and Todd and his associates.³³¹ Thus Straub³³² reported that of 104 patients requiring orthodontic care, 39.4 per cent were definitely allergic and 12.5 per cent possibly allergic. It was also noted that nearly one-fifth of the allergic group had pronounced gingivitis suggestive of allergic etiology. Straub emphasized that the most effective means of reducing the incidence of dentofacial anomalies is early recognition and correction of chronic hay fever or respiratory allergies.

Children with long-standing nasal allergy are usually tired, irritable, and nervous. For this reason, and also because of frequent headaches (frontal and occipital) and impaired hearing, they do poorly in school and often develop antisocial attitudes. If the allergy is severe and occurs early in infancy, the allergic child's mental capacity may be impaired (Todd³²⁹). When the allergic condition is relieved, the child's intelligence often seems to improve rapidly.

Food allergy is especially important in children under 5 years of age; later, dust, feathers, and pollens are the chief offenders. However, the possibility of infectious allergy should always be borne in mind.

For a discussion of diagnosis and treatment of the rhinopathies, the reader is referred to the relevant chapter (pp. 494, 496).

Moore³³³ makes a plea not to remove hypertrophied tonsils in allergic children unless they are chronically diseased or causing some systemic condition such as heart or kidney trouble. They should not be removed before the child is 6 years old. Moore often observed a great increase in symptoms after operation and believes that the lymphatic glands are a protective mechanism against infections and perhaps allergens. Stoesser³³⁴ likewise found that among 214 children whose allergic rhinopathy or asthma appeared to be associated with infections, only 13 were benefited by tonsillectomy and adenoidectomy. In this connection it may be recalled that recent evidence advanced by Ehrlich and others (see page 141) indicates that lymphoid tissue is the site of the formation of antibodies.

HAY FEVER

This disease expresses itself in children precisely as it does in adults. However, when it first occurs in youngsters, it is very often mistaken for a cold or sinusitis.

The mode of treatment of hay fever in children depends on the age of the child. By and large, fair amounts of pollen extracts are quite well tolerated. If the initial difficulty of the child's reluctance to submit to injections can be overcome, any form of therapy may be instituted, as required by a given case. Here again, the present writers prefer the perennial method, with either pollen propeptan therapy or subcutaneous injections, both of which, generally speaking, give very satisfactory results. For the dosage of pollen propeptan for children see p. 558. The maximum dose for parenteral therapy must be carefully ascertained; usually, however, children of 4 or 5 years easily tolerate 5,000 Noon units. If possible, glycerinated extracts should be avoided, since they are definitely more painful and render the treatment more difficult. If there is a marked needle-shyness on the part of either the child or the parents, nasal testing with dry pollens (p. 183) may be employed.

³²⁹ TODD, T. W. *J. Allergy* 9: 234, 1938.

³³⁰ COHEN, M. B. *Angle Orthodontist* 9: 30, 1939.

³³¹ BOWEN, R. C. *Babyeaten Bowen Hay Fever & Asthma Clin Quart* 8: 2, 1939.

³³² TODD, T. W., COHEN, M. B., and BROADBENT, H. *J. Allergy* 10: 246, 1939.

³³³ STRAUB, W. *J. Am. Dent. A* 31: 351, 1944.

³³⁴ MOORE, G. C. *Oklahoma State M. A. J.* 38: 238, 1945.

³³⁵ STOEßER, A. A. *Journal-Lancet* 64: 351, 1944.

BRONCHIAL ASTHMA

Chronic coughs in children are often pre asthmatic manifestations, the symptom is usually a paroxysmal hard dry cough and represents an effort to relieve a tickling sensation in the throat and larynx. Such coughing spells are frequently associated with nasal allergy and are often induced by excessive exercise, laughing, fatigue, and changeable and damp weather. Children who cough without apparent cause should be investigated along allergic lines and appropriately treated, in this way bronchial asthma or chronic respiratory diseases may sometimes be avoided (Marks³⁰⁰⁵).

The clinical picture of asthma in children, especially the younger ones, is somewhat different from that in adults. The highly characteristic subjective complaint of shortness of breath is often lacking in the beginning. The child suffers from a short barking cough that may last for months and is refractory to sedatives, but responds well to epinephrine inhalation. One is sometimes inclined to suspect the presence of pertussis but the characteristic labored inspiration and lymphocytosis are lacking. (We do not here refer to those occasional cases in which the asthmatic cough follows pertussis.) Other children suffer from sudden bronchitides along with severe dyspnea that is not adequately explained by the physical findings. Often an asthmatic bronchitis commonly called spastic bronchitis develops, and in time changes to a typical asthma. Of 100 cases of spastic bronchitis in infancy studied by Koehler and Mar³⁰⁰⁶ 62 per cent developed typical bronchial asthma at some subsequent time—none after more than six years and some almost immediately. A third type also begins with dyspnea but presents bronchiolitis and a temperature elevation of 4 degrees (F) or more. The respiratory rate rises to from 40 to 100 respirations per minute. Persistent coughing, cyanosis, and prostration create an alarming picture, similar to that of a severe pneumonia. Auscultation discloses prolonged expiration accompanied by rhonchi. If the bronchiolitic process progresses, it completely dominates

the picture this readily explains why the diagnosis of asthma is sometimes missed.

Naturally children may also present the other forms of asthma (see p 588). As to the attacks in particular, they are often preceded by prodromes hours prior to the paroxysm, the patient is likely to present increased excitability, headache, a feeling of anxiety, and sometimes even a hallucinatory aura of a strange taste in the mouth. Status asthmaticus very seldom occurs in infants, and even in older children is much less common than in adults.

In children the physical signs during an asthmatic attack often simulate bronchopneumonia especially when fever and leucocytosis are present. According to Cohen³⁰⁰⁷ a special type of pneumonitis occurs differing from bronchopneumonia in pathology, course, prognosis and treatment. In asthmatic paroxysms in children large quantities of mucus are secreted into the respiratory passages. Since this is not easily eliminated it is likely to become inspissated and to form tenacious plugs particularly when dehydration occurs through excessive vomiting. These plugs tend to produce atelectasis and a low grade pneumonitis distal to the plugs may occur. The physical signs at this time may erroneously suggest bronchopneumonia.

In cases in infancy and childhood, the differential diagnosis between bronchial asthma and acute tracheobronchitis is sometimes extremely difficult. The physical signs may be identical in the two conditions. However there is usually more evidence of infection in acute bronchitis, in the latter condition the dyspnea begins and ends gradually, and there are no paroxysms. Moreover, the sputum has different characteristics. In its intensity and duration, the asthmatic cough is very similar to whooping cough, and may indeed assume such proportions that, especially in younger children the physician is erroneously led to assume the presence of a stenosis of high degree and therefore to perform tracheotomy. As a rule, however, the gasping and whistling expiratory wheezing of asthma cannot be confused with the inspiratory sounds of whooping cough. In laryngeal diphtheria, aphonia is

³⁰⁰⁵ MARKS M. B. Arch. Pediat. 29: 697 1942.

³⁰⁰⁶ KOEHLER B. and MAR M. Ztschr. f. Kinderh. 62: 370 1940.

³⁰⁰⁷ COHEN S. New Orleans M. & S. J. 94: 440 1942.

scarcely ever lacking, the development of stenosis is gradual, and the obstruction is both inspiratory and expiratory. The diphtheritic membrane, the presence of a serosanguineous discharge from the nose, and bacteriologic examination will readily provide the diagnosis. Foreign bodies not visible on a roentgenogram (e.g., particles of fruit, peanuts, grain seeds) must be identified by bronchoscopic examination.

There is a type of dyspnea, appearing in early infancy, that is often causally explained on the basis of an enlarged thymus shadow appearing in the chest X ray and is therefore called "thymic asthma." However, the agency of the thymus in the production of these manifestations appears questionable. According to Waldbott,²⁰⁹ the enlarged thymus is a sign of a general allergic reaction, and there is a close relationship between status thymolymphaticus and the allergic state.

Compression of the bronchi by tuberculous lymphadenopathy can often be distinguished from asthma only by means of the response to an injection of epinephrine. Cardiac asthma hardly ever occurs in children, and need not be considered, therefore, for the purposes of differential diagnosis.

Prolonged dyspnea resembling status asthmaticus may be due to any of the following conditions (Ratner²⁰⁹): (1) a foreign body in the esophagus compressing the trachea by its bulk, or by reason of secondary swelling, or both; (2) thymic compression stenosis, (3) subternal goiter, sometimes congenital; (4) lymphadenopathy, the most common site being at the bifurcation of the trachea; (5) cicatricial stenosis due to (a) a suppurating mediastinal gland or (b) persisting presence of a foreign body; (6) foreign bodies in the air or food passages; (7) subglottic laryngitis associated with subglottic edema; (8) papillomas of the trachea or larynx; (9) pulmonary abscess and bronchiectasis; and (10) acute massive atelectasis or collapse of the lung.

The treatment of asthma in children is in no way different from that in adults, except for the fact that, in view of the patient's age, smaller doses of the various drugs must be employed. Small children should never re-

ceive injections of more than 0.2 cc. or 3 minims of 1:1,000 epinephrine at a time; and the total dose over twenty-four hours must never exceed 0.5 cc. (7½ minims). Inhalation of 1:100 epinephrine is of value only when the child can be taught to inhale properly. Ephedrine may serve as a satisfactory substitute, especially in mild attacks. Infants will tolerate small doses, such as 0.008 mg. (1₈ grain), and children of from 1 to 7 years, 0.015 mg. (¼ grain); 0.025 mg. (3₈ grain) may be given to those above this age. In the case of young children, it is preferable to give ephedrine in a 3 per cent aqueous solution, each minim representing approximately 1.30 grain. Demerol is reported by Glaser²¹⁰ to be effective in infants and children in a dosage of 1.5 mg. per Kg. of body weight, and may be mixed in the same syringe with epinephrine. Aminophylline is also useful in children, preferably contained in rectal suppositories. Niacin (nicotinic acid) and niacin amide in doses of 25 to 50 mg orally twice a day before meals give good results in asthma and spastic bronchitis in children (and also, to a lesser extent, in urticaria and dermatitis), according to Surányi.²¹⁰

Morphine and atropine are definitely not to be used. For sedation, 0.5 Gm. (7½ grains) of chloral hydrate by retention enema, or 1.5 Gm. (22½ grains) of urethane by suppository may advantageously be given; in severe cases, a combination of 0.5 Gm. (7½ grains) of chloral hydrate and 1 Gm. (15 grains) of urethane may be administered rectally. In bronchitis asthma, excellent results are often obtained with potassium iodide in doses of 0.5 to 1 Gm. (7½ to 15 grains) daily. It must be remembered, however, that iodine may not be given when there is a goiter, as is often the case in girls. The indications for sulfonamides and penicillin are essentially the same as for adults, the dosage being proportionately smaller.

As for cough medicines, the reader is referred to the prescriptions on page 647, which also include useful emetics, these are of particular help because children are often unable to raise sputum. Syrup of ipecac is a valuable therapeutic aid when the asthma in infants and

²⁰⁹ WALDBOTT, G. L.: *J. A. M. A.* 145: 657, 1935

²¹⁰ RATNER, B.: *J. Allergy* 10: 266, 1929

²¹¹ SCHÖNLY, J.: *Ann. Paediat. (Basel)* 158: 231, 1942.

young children results from bronchial obstruction due to plugs of mucus or exudate (Ratner³³¹ Cooke³³²). An average child 4 or 5 years of age may be given 1 to 2 teaspoons or more in warm water followed by additional warm water to cause vomiting. During the retching a reverse peristalsis of the trachea is set into motion thus dislodging the plug or plugs. The response is often dramatic. If the first dose is not effective it is wise to repeat it and for older children repeated doses may be given until the desired effect is achieved.

Since asthma in young children is often caused by food allergy an elimination diet or propeptan diet should always be tried.

In appropriate cases vaccines have a definite place in treatment. Stoesser³³³ achieved the best results with undernated bacterial antigens and fair results with stock vaccines in children in whom there was every reason to suspect bacterial hypersensitiveness. There was no consistent response to skin testing with bacterial allergens and the results of therapy could not be correlated with the reactions. Autogenous vaccines were ineffective in his hands. Nevertheless the present writers prefer properly prepared autogenous vaccines if a suitable culture can be obtained and especially if positive skin reactions can be elicited.

Breathing exercises are valuable in overcoming the postural and muscular changes that take place in the thorax of the asthmatic child.

Of outstanding importance is recognition on the part of physician and parents of the significance of psychologic factors either in predisposing to or in actually eliciting asthmatic attacks. Anxiety about being unable to attend school with any degree of regularity or to enjoy the normal physical activities and pleasures of childhood fear or worry undue excitement over the disease and particularly the attacks concern about maintaining high standards at school rebellion against what is often considered an excessively protective attitude on the part of the parents—these are some of the problems that can be solved by reassuring the child and educating the parents. Hurst³³⁴ adds that emotional storms of anger,

fright or anxiety often precipitate asthmatic episodes and parental anxiety may produce a more provocative atmosphere than do allergic agents. Hall³³⁵ for one has shown the beneficial effect of psychologic methods in selected cases with particular reference to the child's self assurance the resolution—by education—of psychoneurotic problems and the correction of misunderstandings on the part of siblings and classmates. Jensen and Stoesser³³⁶ also point to the increasing recognition of emotional factors in childhood asthma and cite cases in which their management helped greatly in the control of the disease. The present writers have been applying these principles for many years and are profoundly convinced of their importance.

After an attack the child should of course be examined the initial investigation being directed principally toward the discovery of the probable cause as fully outlined in the section on asthma treatment should then be instituted according to the nature of the underlying factors. If skin testing is impossible or impracticable (lack of cooperation extreme youth of patient generalized dermatitis dermatographism) passive transfer tests may usefully be employed. If skin testing is desired the pressure puncture technic (like that in smallpox vaccination) is recommended because of its rapidity and freedom from pain. A drop of a liquid extract of each allergen is placed on the skin and then direct punctures of the epidermis are made through the droplets being careful to keep all the punctures close together and to avoid too deep penetration in order to prevent bleeding. Three punctures are used for food allergens two for inhalants and one for pollens.

In general the same etiologic factors are responsible for asthma in children as in adults. However certain unusual possibilities should not be overlooked. Thus the present writers have observed a few cases in infants evidently caused by commercial baby powders. The attacks occurred while the powders were being applied to the skin or immediately thereafter. Whether this was caused by the mechanical influences of the powders or by specific hyper-

³³¹HALL, M. B. *B. & M. J.* 2: 110, 1940.

³³²JENSEN, R. A. and STOEßER, A. V. *Am. J. Dis. Child.* 62: 80, 1941.

sensitiveness was not investigated. In any case, it is preferable that asthmatic infants not be freely powdered. Goldberg²³¹ saw a child whose attacks were apparently due to mustard plasters applied each time the patient had bronchitis. It has repeatedly been noted that the percentage of children giving positive reactions and especially those giving marked reactions to skin testing with fungus extracts greatly exceeds that of adults. However, we are not prepared to state that fungi are a more frequent cause of asthma in children.

Furthermore, the general state of health of the asthmatic child must receive careful attention. This means a well-balanced diet, a full quota of supplementary vitamins, iron if there is anemia, and, above all, a great deal of rest. Ratner²³² also recommends desiccated thyroid, depending on the extent of retardation in bone growth or on evidence of a lowered basal metabolic rate in children over the age of 10.

The complications of asthma in children are the same as those of adults. Of the 21 reported cases of subcutaneous emphysema due to asthma, 9 were in patients under 14 years of age (Francis²³³). Pulmonary emphysema and various thoracic deformities are not too infrequent, particularly if the asthma is severe. Spontaneous pneumothorax occurs rarely. Patchy or lobular atelectasis is sometimes seen in grave attacks, although massive atelectasis is unusual. Bronchiectasis is not common. Derbes and Engelhardt²³⁴ found no roentgen or electrocardiographic evidence of cardiac involvement in children with uncomplicated asthma for a number of years. However, they state that this does not militate against the production of heart disease as a consequence of pulmonary fibrosis, emphysema, bronchiectasis, and other pulmonary complications occurring in chronic asthma. Black²³⁵ and Glaser²³⁶ state that they have never seen a child in whom asthma and pulmonary tuberculosis were co-existent.

The prognosis of childhood asthma has not been too thoroughly evaluated. Brock,²³⁷

who studied a series of 351 cases, noted a tendency to improve after the age of 10 years, with spontaneous recovery at the time of puberty in about one-third of the cases, and improvement in a total of 80 per cent. However, it is not unlikely that more prolonged observation would reveal recurrence of the same or other allergic states.

Finally, a note of optimism is of distinct importance in the management of the asthmatic child. To quote Hurst,²³⁸ "every asthmatic can derive much benefit from good advice. He can be taught a way of life; how to avoid the exciting causes of his particular brand of asthma, how to control attacks he is unable to prevent, and, above all, how to be happy in spite of the bad luck of having been born with the asthma diathesis."

2 CUTANEOUS AFFECTIONS

The allergic skin manifestations most commonly encountered in children are infantile dermatitis and lichen urticatus. Since these conditions have been discussed in some detail in the relevant sections, they will not require further consideration here.

However, at this point it seems appropriate to discuss the question of whether or not the skin of infants and young children possesses the capacity of reacting to intracutaneous tests with food proteins or bacterial allergens. Refuting the theory that the skin of children in these age groups is incapable of producing a wheal response, Sulzberger and Baer²³⁹ demonstrated that, even at the earliest ages (from 5 hours to 5 days), infants are able to respond with urticarial lesions to histamine and to codeine. As Zohn²⁴⁰ pointed out, the failure to react to milk, egg, and wheat, as well as to dust, wool, and feathers, supports the view that hypersensitiveness to these common allergens is generally not present at birth, and is not to be interpreted as evidence of a lack of reactivity in the infant's skin. The fact that infants show considerable resistance to many infections, and therefore rarely present exanthematous manifestations, is probably to be explained by the presence of the remaining

²³¹ GOLDBERG, SAMUEL: personal communication.

²³² RATNER, B.: Mississippi Doctor 19, 212, 1941.

²³³ DERBES, V. J., and ENGELHARDT, H. T. J. Pediat. 25, 394, 1944.

²³⁴ ENGELHARDT, H. T., and DERBES, V. J.: ibid. 26, 160, 1945.

²³⁹ SULZBERGER, M. B., and BAER, R. L. Arch. Dermat. & Syph. 41, 1029, 1943.

²⁴⁰ ZOHNE, B. Arch. Pediat. 58, 339, 1941.

antibodies originally transmitted by the mother's blood

3 GASTRO-INTESTINAL TRACT

Gastro intestinal manifestations in childhood are often due to a food allergy. The clinical picture is rather variable. Vomiting, stomach ache, pylorospasm, abdominal cramps, diarrhea, and constipation are the most common symptoms, they may occur alone or may be accompanied or followed by other allergic symptoms, such as rhinopathy, asthma, urticaria, angioneurotic edema, or perioral dermatitis. However, the symptomatology may occasionally be much more dramatic. Thus, Hill²⁹² called attention to a type of milk allergy in which the nursing infant goes into shock and collapse, always with vomiting and often with diarrhea, when it first takes even the smallest amount of cow's milk. This may even lead to death, as shown by 4 cases reported in the literature. Scratch tests are usually negative.

A rather rare occurrence—intestinal hemorrhages as a manifestation of food allergy in infants—was observed in 6 cases by Rubin.²⁹³ All these children had a very strong, usually bilateral family history of allergy, and cow's milk feeding had been started immediately or within a few days after birth. The babies seemed constantly uncomfortable, but this was thought by the mothers to be due to hunger, although it was probably due to abdominal disturbance. Colic first appeared about three weeks after cow's milk feeding was initiated, and became progressively worse, leading to loose stools with mucus and varying amounts of bright red blood. The latter completely disappeared from the stools within forty eight hours after milk had been withdrawn from the diet. The mucus in the stool and the abdominal discomfort ceased shortly afterward.

In addition to these acute gastro intestinal conditions, there are also chronic forms affecting children. One of these is colic, which often recurs at such frequent intervals that it is regarded as a chronic condition. If it stops after the elimination of a certain food from the infant's diet—or from the mother's diet, in the case of a nursing—and reappears after reintroduction of the food item, the

diagnosis of food allergy is justified. According to several authorities, there is good reason to think that the frequency of allergic colic is increased by the current vogue in infant feeding of introducing various new solid foods rather early in infancy, long before there is any real nutritional need for them and before the infant gastro-intestinal tract is prepared for their adequate digestion. Children between the ages of 4 and 12 years not rarely suffer abdominal pain that, because of its chronicity, suggests the possibility of tuberculous mesenteric lymphadenopathy, chronic appendicitis, pyelitis, renal calculus, or any of various anomalies of the digestive tract (Hill²⁹²). This group also includes cases with pylorospasm and recurring attacks of vomiting, commonly called "cyclic vomiting." Six cases of pylorospasm in infants, all due to milk, were reported by McCarthy and Wiseman.²⁹⁴ However, according to Salmi,²⁹⁵ follow up study of 72 cases of pylorospasm in infants, including pyloric stenosis, showed the incidence of allergic diseases in later life not to be significantly higher than in normal control subjects.

Ratner²⁹⁶ divides abdominal pain in children due to food allergy into three categories: (1) abdominal pain as a minor symptom, sometimes in conjunction with asthmatic or urticarial attacks, (2) recurrent abdominal pain, the most frequent type, usually occurring in association with other allergic manifestations, and in children with a history of colic or vomiting in infancy. The pain is cramp-like and usually localized in the region of the umbilicus, but may also be present in the epigastrium, paraumbilical region, or right lower quadrant. It is accompanied, as a rule, by gastro intestinal symptoms such as diarrhea, flatulence, mucous stools, nausea, vomiting, or even constipation, and (3) severe abdominal pain simulating an acute surgical condition of the abdomen. However, it must be remembered that an allergic condition may lead to irreversible changes and require surgical intervention. Ratner attributes the mechanism of the pain to spasm of gastro intestinal smooth muscle, or wheal formation in the gastro intestinal wall, or spasm of the small

vessels of the gastro-intestinal walls, or a combination of these factors. Roentgen findings of pylorospasm, delayed emptying of the stomach, or hypertonicity and hyperperistalsis of the intestine following a test meal of the offending food, are of diagnostic value. Therapeutic trial of epinephrine and atropine or its derivatives will also help to clarify the diagnosis.

McKhann et al.²³⁹ advance suggestive evidence that gastro-intestinal allergy bears a causal relationship to the celiac syndrome. Two cases showed positive skin reactions to banana, and elimination of the suspected foods in 4 cases resulted in definite improvement, including an increase in the absorption of fats and glucose from the gastro-intestinal tract.

Two instances of a syndrome consisting of clay-colored stools without jaundice but accompanied by abdominal pain and presumed to represent hepatitis, were considered by Clein²⁴⁰ to be definitely due to food allergy.

According to McLendon and Jaeger,¹⁰⁵ the symptoms of milk intolerance include, in order of frequency, constipation, anorexia, abdominal discomfort, pallor, fatigue, disturbed sleep, recurrent diarrhea, urinary disturbances, and geographic tongue. The history characteristically contained the following features: excessive milk ingestion on the part of the mother during the latter months of gestation, early ingestion of cow's milk by the infant, the colic syndrome, frequent formula changes with only transient relief, diminution of the acuity of the symptoms as solid foods were

added to the diet, and the appearance of some of the above symptoms as the child developed.

For a further discussion of the subject of gastro-intestinal allergy, including methods of testing and treatment, the reader is referred to chapter XXIII. However, the writers would like to underscore the excellent results which they so uniformly obtain in cases of intestinal food allergy with the propeptan diet (see page 220).

4. SKELETON

Todd¹²¹ is inclined to interpret the roentgenologically demonstrable scorings in the lower ends of the tibia and radius as evidence of increased calcium deposition, due to temporarily diminished growth that is attributable, in turn, to nutritional disturbances associated with gastro-intestinal allergy. Cohen and Friedmar²⁴¹ even suggested using roentgenograms showing such scorings as an index of effective control of gastro-intestinal allergy, and recommended that a restricted diet be enforced until no new scorings could be seen. However, Chobot and Merrill²⁴² point out—and correctly, in the writers' opinion—that similar roentgenologic shadows may be observed in growing children as a result of any of a great variety of pathologic conditions, such as acute infections, deficiency diseases, starvation, and dehydration. It is therefore hazardous to make a diagnosis of allergy solely on the evidence of these bone scorings.

²³⁹ TODD, T. W. *J. Pediatr.* 3: 415, 1933.

²⁴¹ COHEN, M. B., and FRIEDMAR, S. *J. Allergy* 9: 54, 1937.

²⁴² CHOBOT, R., and MERRILL, E. F. *Ibid.* 8: 338, 1937.

ALLERGY IN THE AGED

THE view is widely held that allergic manifestations are a prerogative of childhood youth and middle age. Moreover it has frequently been claimed that with advancing age certain allergic diseases such as hay fever and asthma spontaneously disappear or at any rate become far less severe. Before indulging in any such generalization it might be informative to examine the factors affecting a given case. The aged worker who after his retirement is no longer exposed to the irritating vapors in his place of work will unquestionably find his bronchitis asthma considerably unproved. The farmer who now leaves the work in the fields to his sons will find that his hay fever attacks are not as severe as they used to be. Examples of this sort show that certain predisposing and contributory factors exert a very considerable influence. Furthermore many people become much less active as they grow older or are far less exposed to excitement. Aside from such considerations however it may be said that many men and women over 60 years of age are still markedly allergic indeed they sometimes become allergic for the first time at this age. In the sections on hay fever and asthma the writers have mentioned cases in which initial attacks of these diseases were suffered by patients of 70 years or older. Urticaria is also frequently encountered in elderly people. Migraine on the other hand generally becomes milder or disappears completely after the menopause. Likewise although it is generally true that the skin of the aged shows a diminished reactivity a recent case report by Wiseman and McCarthy Brough³³²⁴ indicates that this need not necessarily be true.

The most important allergic manifestation encountered in the old age group is asthma. This is usually a bronchitis asthma or a non-specific (pathergic) asthma. According to Mueller Deham and Rabson³³²⁵ bronchial asthma is not a rare occurrence in the aged. The attacks vary from single typical paroxysms to continuous seizures characteristic of status asthmaticus. The clinical syndrome is often mistaken for cardiac asthma or for respiratory distress due to cerebral arteriosclerosis or hypertension. Many attacks are actually of a mixed type. The principal means of differentiation between cardiac and bronchial asthma are circulation times and the response to therapy. If the measures usually successful in combating bronchial allergy are effective and cardiac therapy alone is unavailing it seems likely that the case is one of bronchial asthma. On the other hand it should be borne in mind that cardiac stimulants are indicated in every case of severe or persistent bronchial asthma. Black³³²⁶ estimates that not more than 5 per cent of those developing dyspnea after 50 years of age are asthmatic.

Another important manifestation of hypersensitiveness in this age period is rhinopathy. Since this disease was fully covered in the relevant section with full consideration of the condition in older people no further discussion is necessary here.

In conclusion it should be pointed out that age alone is no valid basis for rejecting the possibility of an allergic mechanism in a given case. The final decision as to whether or not the disease is based on hypersensitiveness must always depend on the results of the appropriate studies rather than on considerations of age.

³³²⁴ WISEMAN J R and MCCARTHY BROUGH M P J. *Allergy* 16: 20, 1941.

³³²⁵ MUELLER DEHAM A and RABSON S M. *Internal Medicine* 30: 40, 1942.

Appendix

Clinical Record for Allergy Patient

Name	Date of Admission	No.
Address	Phone no	Age
Occupation	Race	M F S M W D
Referred by	Address	
Diagnosis		

History taken by Dr.	Examined by Dr.
----------------------	-----------------

Chief Complaint:

History of Present Illness:

Past Medical History

Allergic Diseases: hay fever, rhinopathy, asthma, allergic cough
 infantile dermatitis, urticaria, papular urticaria, angioneurotic edema, neurodermatitis, contact dermatitis, poison ivy dermatitis
 food allergy, cyclic vomiting
 drug allergy (including sulfonamides and penicillin)
 serum and toxoid reactions
 recurrent hydarthrosis
 allergic conjunctivitis
 migraine, epilepsy

Diseases of Childhood: chicken pox, croup, diphtheria, German measles, measles, rheumatic fever, scarlet fever, whooping cough

Infectious Diseases: sore throat, tonsillitis, tracheitis, laryngitis, bronchitis, sinusitis, influenza (grippe), otitis media, mastoiditis
 abscessed teeth, pyorrhea alveolaris
 pleurisy, pneumonia, tuberculosis
 dysentery, typhoid fever
 arthritis, rheumatism
 infections of kidneys, pyelitis, cystitis, urethritis
 epididymitis, prostatitis, seminal vesiculitis
 oophoritis, salpingitis, endometritis
 furunculosis, cellulitis, paronychia, hydrosadenitis axillaris, lymphadenitis, osteomyelitis
 malaria
 venereal diseases

Infe tations thread p n tape orms

Gastro intest nal Diseases nd gest ion gastric d stress or pa n hea thurn belch n nausea vom t n_o rectal
flatus colic d arrhea const pat on hemo rho ds d seases of l er o gall bladder

Metabolic D seases thyro d p tu tary d abetes gout obes ty

Ski D seases (other than dermat s) part ular y fungous nfect on

Gynecologic a d Obstet ic Menstruat on Regu arity Amount

Menstrual D stur ances

Number of P egnanc es

Compl cations of p egnanc (vom t ng eclam y s a

Operat o s tons ls nasal s nus ear dental gall bladder stomach ntest na append x ova an ute ne

History of Ser Treat e t (nc ud ng tetanus ant tox n d phther a ant tox n pneumon a serum etc)

Fam ly History of Allergy

Soc al H story

Ho e Type of bu l d ng

Type of heating

Methods of clean ng (vacuum cleaner mop broom etc)

Does pat ent have a bedroom for h mself?

Pets

Cut flo ers or p ants in house

Floor cover ngs

In ect c des used

Il ork Natu e of occupat on

Present

Prev ous

Hobbies

Habit Det P ote n

Sa t

Fat

Coffee

Carbohyd ates

Tea

Sp ces

Cola everages

V tan ns

Alcohol

Tobacco

Dr g (for headac es nd est on const pat on dysmenorrhea asomn a etc)

E ot onal L fe

Is pat ent nervous exc tal le orr some

Is there fam y fr ct on?

Relat onsh p to emp o e and fe o orkers

Econom c stress?

Spec al History for Ch ldren

Age of father of mother

Their emot onal relat onsh p (good cool quar elsome divorced)

Re at ves n the house (grandparents aunts etc)

Rank in order of b th (only ch d fi st born late born)

Sex d str but ion of s bl ngs

Attendance at k n derga ten or school

Att tude of teachers

What pun shment s used at home?

Spank ng?

Scep In o n room?

th s bl ngs

w th parents?

Nervous man festat ons (langua e appet te vom t ng defecat on enu es s)

Emot onal l fe

Fears

PHYSICAL EXAMINATION

Ht.	Wt.	P.	B.P.
General appearance and nutrition			
Skin (ichthyotic, seborrheic, hypodrotic)			
Nose:			
Mouth:			
Teeth, tongue, throat.			
Respiration: type, rate, rhythm, dyspnea, orthopnea, α auscult, wheezing			
Lungs:			
Heart:			
Abdomen:			
Nervous system (including vasomotor responses)			
Endocrine system			

Sites of Focal Infections

(Underline any present infectious disease)

Eyes: dacryocystitis

Ears: otitis externa, otitis media

Sinuses: frontal, maxillary, ethmoids, sphenoids

Teeth: pyorrhea alveolaris, periodontal pocket, periodontitis

Pharynx: adenoids, tonsils

Bronchi: bronchitis, bronchiectasis

Gastro-intestinal Tract: gastro-enteritis, appendicitis, colitis, proctitis, dysbacteria (abnormal intestinal flora)

Gallbladder: cholecystitis

Urinary Tract: pyelonephritis, cystitis, urethritis

Genitalia: prostatitis, vesiculitis

endometritis, endocervicitis, salpingitis, oophoritis

Bones and Joints: osteomyelitis, infectious arthritis

Skin: pyoderma, paronychia (fingers, toes), fungous infection

BRONCHIAL ASTHMA—RHINOPATHY

	Asthma	Rhinopathy
Date of onset		
Type of onset		
sudden insidious		
Did the first attack follow		
acute disease (upper respiratory infection cold grippe pneumonia whooping cough)		
chilling or wetting of body physical overexertion emotional upset change of diet		
prolonged automobile ride work in barn barnyard or field		
Duration of attacks		
Frequency of attacks		
Symptoms of attacks		
wheezing shortness of breath cough expectoration nasal symptoms		
Symptoms between attacks		
especially chronic bronchitis nasal obstruction		
Nature and amount of sputum		
mucoid viscous purulent fetid blood streaked		
Nature of nasal discharge		
serous mucoid purulent		
Do the attacks or symptoms occur		
at certain seasons of year		
at certain times of day or night		
Do the attacks or symptoms occur		
on change in weather		
in dry or damp weather		
on windy or dusty days		
in cold or heat		
on exposure to house or occupational dust		
after respiratory infections		
in presence of animals		
horses cows sheep goats hogs dogs cats rabbits mice rats birds canaries		
bees mosquitoes other insects worms		
on occupational or personal contact with animal products		
animal hair pelts furs feathers dust dander whisks brushes bristles sheep's		
wool silk linen in ties in straw upholstered furniture stored foods		
due to odors, vapors or smoke		
animal odors perfumes fresh paint turpentine naphthalene kitchen odors		
(grease vapors from baking or roasting) tobacco smoke motor fumes (gasoline		
oil vapors) tar factory smoke		
after taking certain foods and drugs		
during gastro intestinal disorders		
during excitement		
during physical exertion		
including prolonged laughing or coughing		
Are attacks or symptoms related to particular places?		
At home		
bedroom living room kitchen cellar attic		

	Chicken feathers	Goose feathers	Down	Kapok	Horse hair	Flax	Sheep Wool	Felt	Cotton	Rabbit Hair	Guinea Pig Hair	Straw	Rubber	Other
Composition of mattresses														
pillows														
cushions														
featherbeds														
bed covers														
quilts														
blankets														
upholstery in home														
upholstery in car														
										Asthma	Rhinoopathy			
At work:														
office, store, factory, stable, barn														
Out of doors:														
garden, fields, woods														
Effect of change of residence.														
travel, vacation, seashore, mountains, etc														
Effect of menstruation, pregnancy, menopause														
Treatment or remedies with complete or partial relief.														
Treatment without effect.														

POLLINOSIS

Onset Year spring season (from to)
 early summer season (from to)
 fall season (from to)

Type of Symptoms during Season

sneezing nasal obstruction conjunctivitis asthma eczema urticaria digestive disturbances migraine vertigo neuritis
 other symptoms

Effect of Changes in Residence

vacation seashore mountains sea voyage

Is the patient entirely free of nasal and pulmonary symptoms outside the hay fever season?

(If not give full information on the asthma rhinopathy form)

Previous treatment and results

SPRING SEASON*

	Date	Scratch Test	Nasal		Intracut Test	Strength	Remarks
			R	L			
Alder							
Box Elder							
Cottonwood							
Elm							
Maple							
Poplar							
Willow							
Ash							
Black Walnut							
Beech							
Birch							
Hickory							
Locust Black							
Oak							
Pine							
Sycamore							

EARLY SUMMER SEASON*

Brome Grass							
Canada Blue Grass							
Dandelion							
English Plantain							
Fescue Grass							
June Grass							
Orchard Grass							
Quack Grass							
Red Clover							
Red Top							
Rye Grass							
Sweet Vernal Grass							
Timothy							
Oat							
Rye							
Wheat							

LATE SUMMER AND FALL SEASON*

Ragweed Dwarf							
Ragweed Giant							
Cocklebur							
Goldenrod							
Lamb's Quarters							
Marsh Elder							
Pigweed							
Dahlia							
Daisy							
Sunflower							
Corn							
Crab grass							

* Pollens to be selected in accordance with the local type in which patient resides. Those given here are for the Philadelphia area.

STUDIES SUGGESTED

(Check those desired)

Scratch Tests. Spring-Summer-Fall Pollens, Epidermals, Inhatants, Food-, Molds
 Intradermal Tests. Spring-Summer-Fall Pollens, Epidermals, Dust, Foods, Bacteria, Tuberculin, Molds
 Patch Tests. Chemicals, Cosmetics, Drug-, Epidermals, Fabrics, Pollen, Plants
 Passive Transfer. Blood serum, Blister fluid
 Nasal Tests
 Bronchial Tests
 Environmental Tests. Day Trial, Night Trial
 Food Diary
 Elimination Diet
 Propeptin Diet
 Tests to Physical Agents
 Sputum, Nasal Secretion
 X-ray of Chest, Sinuses, Teeth
 Vital capacity
 Bronchoscopy
 Blood Count, Chemistry, Serology
 Sedimentation Rate
 EKG, Circulation Time
 Basal Metabolic Rate
 Fractional Gastric Analysis
 Biliary Drainage, Liver Function Tests
 Urine, Stool, Porphyrin

Consultations:

Medical
 Nose and Throat
 Gynecologic
 Gastro-intestinal
 Dental
 Endocrine

SKIN TESTS

Date	Sk n Site	Allergen (0.02 cc.)	Scratch Test 20 min	Intracut Test 20 min	Strength	Retest	Remarks
		Diluent (control)					
		EPIDERMALS					
		cat hair					
		cattle hair					
		chicken feathers					
		dog hair					
		goat hair					
		goose feathers					
		guinea pig hair					
		hog hair					
		horse dander					
		human dander					
		rabbit hair					
		sheep wool					
		MISCELLANEOUS IN					
		HALANTS					
		castor bean					
		cottonseed					
		flaxseed					
		glue					
		house dust stock					
		autogenous					
		kapok					
		karaya gum					
		ornis root					
		pyrethrum					
		silk					
		tobacco					
		FOODS					
		<i>Fish and seafood</i>					
		clam					
		crab					
		flounder					
		haddock					
		lobster					
		mackerel					
		oyster					
		salmon					
		shrimp					
		tuna fish					
		<i>Meats</i>					
		beef					
		lamb					
		pork					
		<i>Fowl</i>					
		chicken					
		duck					
		goose					
		turkey					

SKIN TESTS—Continued

Date	Skin Site	Allergen (0.02 cc.)	Scratch Test 20 min.	Intracut. Test 20 min.	Strength	Retest	Remarks
		<i>Eggs</i>					
		white					
		yolk					
		<i>Dairy products</i>					
		milk, cow's					
		cheese, American					
		<i>Cereals</i>					
		barley					
		buckwheat					
		corn					
		oat					
		rice					
		rye					
		wheat					
		<i>Vegetables</i>					
		asparagus					
		bean, navy					
		bean, soy					
		bean, string					
		cabbage					
		carrot					
		cauliflower					
		celery					
		cucumber					
		lettuce					
		onion					
		pea					
		potato, white					
		spinach					
		tomato					
		<i>Fruits</i>					
		apple					
		banana					
		grape					
		grapefruit					
		orange					
		peach					
		pear					
		pineapple					
		plum					
		strawberry					
		<i>Nuts</i>					
		cocoanut					
		peanut					
		walnut, English					
		<i>Beverages</i>					
		cocoa					
		coffee					
		hops					

SKIN TESTS—*Concluded*

Date	Skin Site	Allergen (0.02 cc)	Strength	Intradermal Test		Subcutaneous Test		Reaction	Remarks
				20 min	24	20 min	24 h		
		BACTERIALS							
		Staphylococcus aureus							
		Staphylococcus toxod							
		Streptococcus haemolyticus							
		nonhemolyticus							
		viridans							
		Micrococcus catarrhalis							
		Pneumococcus old tuberculin	1 1 000 000						
			1 100 000						
			1 10 000						
		FUNGI—MOLDS							
		Alternaria sp							
		Aspergillus fumigatus							
		Cephaosporium							
		Epidermophyton inguinale							
		Hormodendron							
		Monilia albicans							
		Mucor plumbeus							
		Penicillium digitatum							
		Trichophyton interdigitale							
		yeast—baker's							

SUMMARY

*Diagnosis**Present illness**Past history of allergy**Family history of allergy*

<i>Examination</i>	Ht.	Wt.	Pulse	B.P.
nose: clinically				
cytologic				
bacteriologic				
sinuses: clinically				
X-ray				
lungs: clinically				
X-ray				
bronchoscopic				
vital capacity				
sputum: microscopic				
bacteriologic				
heart: clinically				
electrocardiogram				
circulation time				
teeth: clinically	.			
X-ray				
tonsils				
eyes, ears				
stomach, intestines				
gallbladder				
skin				
neurologic				
blood. Hgb	R.B.C.	W B C.	diff.	
serologic		chemistry		
		B M.R.		
urine				

Positive allergic reactions to

pollen

molds

dust

epidermals

other inhalants

foods

drugs

serum

contactants

bacteria

tuberculin

Type of Treatment and Results

TABLE OF CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING**

KEY TO ABBREVIATIONS AND SYMBOLS

acet = acetone	pdr = powder
alc = alcohol 70 per cent	pet = petrolatum
aq = aqueous	prop = proprietary preparation
chlor = chloroform	sat = saturated
c o = castor oil	sol = solution
controls = perform control tests on normal subjects	* We suspect that the concentration given is too strong for routine testing
dext = 15 per cent dextrose solution	† This substance has been known to cause sensitization of the eczematous type even after a single application to normal skin
Ger = German	
o o = olive oil	

Substance		Dilution (per cent)	Vehicle
Acetanilid	pdr	as is	
Acetic acid		3	aq
Acetone		as is	
Acetphenetidin	pdr	as is	
Acridine	pdr	pure	
Agente Alba (prop.)		75	pet
Agente Alba (prop.)		20	alc
Alcohol U S P		70-95	
Alcohol denatured		as is	
Aldehyde amines		as is	
Alizarin		pure	
Alizarin 778		1	alc
Alizarin red 1034	pdr	as is	
Alizarin sulfate		10	aq
Alkaloids as salts		1	aq
Allspice		as is	
Almond oil		as is	
Alpha naphthylamine		pure	
Alum		10	aq
Aluminum scrapings		as is	
Aluminum acetate		10	aq
Aluminum chloride		2	aq
Alypin		1	aq
Amber oil of		1	alc
Amido azobenzol		2 10	o o
Amido azotoluene hydrochloride		1	aq
Amidol		5	aq
Amidophenol (ortho meta or para)		2 10	pet
Amines		2	pet
Amino azotoluene		2	alc
Amino azotoluene	pdr	as is	
Aminodacrylic acid		1	alc
Aminopyrine		as is	
Ammonia		1-2	aq
Ammonium bichromate		0.5	aq
Ammonium bichromate		0.5	pet
Ammonium carbonate		15	aq
Ammonium chloride		3	aq

** Based on tables in Rostenberg A. Jr. and Sulzberger M. B. J. Invest. Dermat. 2: 53 1939 and Sulzberger M. B. and Baer R. 1943 Year Book of Dermatology and Syphilology p. 7

PATCH TESTING—Continued

Substance		Dilution per cent	Vehicle
Ammonium fluoride		0.5-2	aq
Ammonium nitrate		10	aq
Ammonium persulfate		1-5	aq
Ammonium sulfate		10	aq
Amyl acetate		pure	
Analgesics		as is	
Anesthetics		5	pet.
Aniline		10-25	o.o
Aniline black 870	pdr	pure	
Aniline brilliant green	pdr	pure	
Aniline dyes		2	o.o
Aniline dyes		2	pet
Aniline dyes	pdr	pure	
Anise seed oil		25	co.
Anthracene		pure	
Anthralin (1.8 dihydroxyanthranol)		0.1	pet
Anthraquinone, powder		pure	
Anthraquinone blue S R-1059		pure	
Anthrarobin		3	pet
Antihidrotics (prop.) (controls)		as is	
Antimony chloride		2	aq
Antimony oxide		pure	
Antipyrine		as is	
Aquaphor (prop.)		as is	
Aqua Velva (prop.)		as is	
Argyrol		10	aq
Arnica, tincture of		20-25	pet
Arnica, tincture of		20-25	alc.
Armig's tincture, modified (anthrarobin, tumenol, glycerin, spirits ether)		as is	
Aromatic oils		1	alc.
Arsenious trioxide	pdr	pure	
Asphalt (no adhesive covering)		as is	
Aspirin		as is	
Atropine sulfate		1	aq
Auto lubricating oils		60	o.o
Auto polishes (controls)		as is	
Azochloramid		0.2	tracetin
Bakelite (scrappings)		as is	
Baking powder		as is	
Baking soda		as is	
Balata (rubber)		as is	
Balsam of Peru		10	pet.
Banana peel oil		pure	
Barbiturates		as is	
Barium hydrate		0.5	aq
Barium sulfate		as is	
Barley oil		pure	
Bayberry, oil of		25	o.o
Bayberry, oil of		25	pet.
Beef fat oil		pure	
Beef salt		5	aq
Beeswax		pure	

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Beetle (prop)	pure	
Benzaldehyde	10	aq
Benzanthrone	pure	
Benzidine	pure	
Benzine	60	o o
Benzocaine	5	pet
Benzoic acid	6	pet
Benzoic anhydride	10	aq
Benzol	60	o o
Benzoquinone	1	aq
Benzoyl amino metoxy chlor anthraquinone	2	o o
Benzyl alcohol	10	pet
Benzyl benzoate	10	aq
Benzyl chloride	5	aq
Benzyl cinnamate	10	pet
Bergamot oil of	10	pet
Betahydroxy anthraquinone	1	alc
Betanaphthol	10	o o
Beta phenylacrylic acid	5	pet
Bismarck brown 331	pure	
Bismogenol	as is	
Bismuth colloidal solution	as is	
Bismuth oxychloride	5	pet
Bismuth subnitrate	25	pet
Bismuth subsalicylate	14	o o
Black flag (prop)	as is	
Black flag (prop)	25	o o
Black rouge	as is	
Bleaching powder (controls)	10	aq
Blueing	as is	
Borax	sat sol	
Boric acid	pure	
Boric acid ointment U S P	as is	
Borocaine	1	aq
* Brake fluid (prop) (controls)	as is	
Brass metallic scrapings	as is	
Brass weldings scrapings	as is	
Brass polish	10	aq
Brazil wood (redwood)	as is	
Brazil nut	as is	
Brilliant cresyl blue BB(L) 877	pure	
Brillo (prop)	as is	
Bromo acid 768	pure	
Bronze liquid paint	as is	
Burow's solution	10	aq
Butesin	1	alc
Butesin picrate ointment (prop)	as is	
Butyl acetate	pure	
Butyl alcohol	pure	aq
Butyric acid	1	
Cade, oil of	5-10	pet
Cadmium orange	pure	
Cadmium red, deep	pure	

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Cadmium red, light	pure	
Caffeine	1	aq.
Calcimine	as is	
Calcium arsenate	pure	
Calcium carbonate	3	aq
Calcium chloride	2-10	aq
* Calcium cyanamide (crude)	10	aq.
Calcium fluoride	0.5	aq
Calcium hydrate	0.125	aq
Calcium nitrate	10	aq
Calcium oxide	10	aq.
Calcium phosphate	10	aq
Calcium sulfide	1	aq
Calmitol ointment (prop.)	as is	
Calomel	pure	
Camomile, oil of	25	c o
Camomile, oil of	25	pet
Camphor	pure	
Camphor ice (prop.)	as is	
Camphor, oil of	10	pet
Camphor, spirits of	as is	
Canada balsam	as is	
Cantharides, tincture of	1	alc.
Capicum, tincture of	1	alc
Caraway seed, oil of	25	c o
Caraway seed, oil of	1	alc
Carbazole	pure	
Carbon	as is	
Carbon disulfide	60	o o
Carbon paper	as is	
Carbon tetrachloride	pure	
Carborundum	as is	
Cardamon	as is	
Cashew nut shell oil	3-5	alc
Cassia, oil of	1	alc.
Catile (prop.)	as is	
Cement (controls)	as is	
Ceresin	pure	
Charcoal	as is	
Chestnut, extract of	10	aq
Chicken fat oil	pure	
Chloral hydrate	10	aq
Chloramine	0.5-1	aq.
Chlorbenzene	5	o o.
Chlorexone	2	alc.
Chlorinated lime	2-10	aq
Chlorinated naphthalene . .	pure	
Chloroform	40	o o
Chocolate	as is	
Chrome alum	as is	
Chromic acid	0.5-1	aq.
Chromium chloride	2	aq.
Chromium potassium sulfate	10	aq

PATCH TESTING—*Continued*

Substance		Dilut on (per cent)	Veh cle
Chromium sulfate		2	aq
Chrome yellow	pdr	pure	
Chrysarobin		1-5	pet
Chrysoidin brown	pdr	pure	
Cinnabar		3	pet
Cinnamic acid		5	pet
Cinnamon	pdr	as is	
Cinnamon, oil of		5	o o
Cinnamyllic acid		5	pet
Citric acid		1	aq
Citronella		as is	aq
Cleaning fluids noninflammable (prop) (controls)		as is	
Cleaning fluids inflammable (prop) (controls)		60	o o
Clorox (prop)		10	aq
Clothing and clothing materials		as is	
Cloves	pdr	as is	
Cloves oil of		25	c o
Cloves oil of		1	alc
CN (prop)		1-10	aq
Coal tar crude		5-10	pet
Cobalt chloride		2	aq
Cobalt oxide		pure	
Cocaine		1	aq
Cochineal natural 932		10	aq
Cocoa		as is	
Cocoonut oil of		pure	
Codeine sulfate		1	aq
Cod fish oil		pure	
Cod liver oil		as is	
Coffee		pure	
Coffee oil of		pure	
Collodion		as is	
Colza oil		as is	
Copal		pure	
Copper chloride		1	aq
Copper cyanide	pdr	pure	
Copper scrapings		as is	
Copper sulfate		5	aq
Coriander oil of		1	alc
Cosmetics (controls with hair tonics etc cuticle softeners etc are usually primary irritants)		as is	
Cotton seed oil		pure	
Crayons		as is	
Creosote		10	o o
Cresol		0-5-1	aq
Crude oil		as is	
Crystal violet 681		2	aq
Cumaron		pure	
Cutch		pure	
* Cuticle remover (controls)		as is	
Cyclohexanol		50	o o
Damar (resin)		pure	
Decahydronaphthalene (dekalin)		50	o o

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Dekalin (Ger prop. name for a turpentine substitute)	50	o o
Denatured alcohol (controls)	as is	
Deodorants	as is	
Depilatories (controls)	as is	
Dermatol (Ger prop dusting powder)	pure	
Dextrin	50-80	aq
Diacetylamidoazotoluol	2	pet
Dianisidine	pure	
Diazonium salts	1	pet
† Di-beta naphthyl paraphenylene-diamine	pure	
† Dichlorbenzene	5	chlor
Dichlorbenzidine	5	alc
Dichloronite benzine	10	aq
1-2 dichloronitrobenzene	1	acet.
1-2 dichloronitrobenzene	1	acet
Diethylanis-ethanol	1	aq
Diethylene glycol	10	aq
1-8 dihydroxy-anthranol	0.1	pet
1-2 dihydroxy-anthraquinone	0.5	alc.
1-8 dihydroxy-anthraquinone	0.5	alc.
1-4 dihydroxy-anthraquinone	0.5	alc
Dimethyl amine	pure	
Dimethyl aniline	10-25	o o
† 1-2-4 dinitrochlorbenzene	1	acet
Dinitroresol	5	chlor
2-4 dinitrophenol	10	aq
Dinitrotoluol	sat	alc.
Di-orthotolyl guanidine	pure	
Di-orthotolyl thio-urea	pure	
Diphenyl	pure	
Diphenyl-guanidine	2-10	o o
Dithio acids, salts of	pure	
Ditolyl amines	pure	
Dragon's Blood (prop.)	as is	
Dusts	as is	
Dust oil	as is	
Dutch Cleanser (prop.)	as is	
Dyes, lakes and toners	pure	
Earthy pigments	pure	
"El Key" Insecticides (prop.)	50	o o
Elon, fresh (prop.)	0.5	aq
Emetine hydrochloride	pure	
Enamel (controls)	as is	
Eosin	as is	
Ephedrine	1	o o.
Erythrosin	as is	
Esbach's reagent	2	aq.
Essential o.s (controls)	1	alc.
Esters	pure	
Ester gums	pure	
Ether	60	o o.
Ethyl acetate	pure	
Ethylene dichloride	50	o o.

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Ethylene dichloride	0.1	alc
Ethyl mercury chloride	0.5	aq
Ethyl mercury phosphate	0.5	aq
Eucalyptus oil of	1	alc
Eye lotions cosmetics shadows	as is	
Fat oil of	5	pet
Fenchyl alcohol	pure	
Fennel oil of	1	alc
Ferric chloride	2	aq
Ferric ferrocyanide	as is	
Ferric sesquichloride	10	aq
Ferrosulfate	10	aq
Fertilizers most commercial preparations (controls)	as is	
Fixative	as is	
Flavoring oils (controls)	2	alc
Flit (prop.)	25	o o
Floor wax (controls)	10	o o
Flour all kinds	as is	
Flour bleaches (controls)	as is	
Flowers fresh dry artificial (controls)	as is	
Fluorene	pure	
Fluorescein	1	alc
Flux aluminum	as is	
Flux iron	as is	
Flycide (prop.)	25	o o
Food any kind (except rinds of certain fruits spices mustard etc.)	as is	
Formaldehyde	5	sq
Formic acid	1	aq
Fowler's solution	75 is	
Frostilla (prop.)	as is	
Fruit citrus peel (controls)	as is	
Fuchsin	10	aq
Furfural	pure	
Furniture polish (controls)	10	o o
Furs any dyed natural	as is	
Fustic (yellow wood)	pure	
Fustic (yellow wood)	sat	aq
Gallate	as is	
Gasoline regular ethyl	60	o o
Gentian violet (BDC) 680	2	aq
Ginger	pure	
Ginger oil of	25	c o
Glue	as is	
Glycerin	pure	
Glycerin oil	as is	
Glyptal (prop.)	pure	
Gold Dust (prop.)	as is	
Gold sodium thiosulfate	0.5	aq
Grapefruit peel oil (controls)	pure	
Graphite	as is	
Greases	as is	
Grease solvents most proprietary (controls)	as is	
Guanidines	pure	

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Gum arabic	as is	
Gun grease	as is	
Gun powder	as is	
Gutta-percha	as is	
Gutta siac (a rubber)	as is	
Hair, all kinds, natural, dyed	as is	
Hair dyes	as is	
Hair lacquers	as is	
Hair tonics, lotions (controls)	as is	
Hat glazing, sizing or lacquers for (controls)	as is	
Hempseed oil	as is	
Henna, Egyptian	as is	
Henna, white	as is	
Hexahydrophenol	50	o o
Hevalin (C_6H_4OH)	50	o o
Hexamethylene tetramine	pure	
Hexylresorcinol	as is	
Histamine (acid phosphate)	0.1	aq
Homatropine	1	aq
Hydrochloric acid	1	aq
Hydrofluoric acid	0.2	aq
Hydrogen sulfide	10	aq
Hydroquinone	5	aq
Hydroterpens	50	o o.
Hydroxymercurichlorphenol	0.5	aq
Hydroxymercuricresol	0.5	aq
Hydroxymercurinitrophenol	0.5	aq
Hypnotics	as is	
Ichthyol	5-10	pet.
Indigo	10	aq
Indole	sat	aq
Inecto A (prop. hair dye)	as is	
Inecto B (prop. hair dye)	as is	
Ink eradicators (controls)	as is	
Inks	as is	
Iodine crystals	0.5	pet.
Iodine crystals	1	alc.
Iodine, tincture of, U.S.P. (do not cover! simply paint on)	as is	
Iodobismutol (prop.)	as is	
Iodoform	25	pet.
Iridium chloride	10	aq
Iron chloride	2	aq
Iron, metallic scrapings	as is	
Iron sulfate	10	aq.
Istuzin, 1,8-dihydroxy-anthraquinone	0.5	alc.
Javelle water	10-20	aq.
JO Roach Powder (prop. insecticide)	as is	
Juniper, oil of	25	c.o.
Juniper, oil of	1	alc.
Kainit (Ger. prop. fertilizer)	10	aq
Karbolinum (Ger. prop. wood preservative)	50	o o.
Kerosene	60	o o
Kill It (prop. insecticide)	as is	

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Lac dyes	50	pet
Lacquers (controls)	as is	
Lakes	50	o o
Lakette	as is	
Lanolin	as is	
Lard	as is	
Larocaine	1	aq
Larvex (prop.)	10	o o
Latex	as is	
Laurel oil of	25	c o
Lavender, oil of	1	alc
Lead, white	as is	
* Lead, red	as is	
Lead arsenate	pure	
Lead arsenate	5	aq
Lead azide	pure	
Lead chloride	pure	
Lead styphnate	pure	
Lead subacetate	0.2	aq
Lead sulfide	2	aq
Leathers, natural, tanned, dyed, imitation	as is	
Lemon, oil of (controls)	1	alc
Licorice	as is	
Lime, burnt	10	aq
Lime, slaked (controls)	as is	
Linalool	1	alc
Linseed oil	as is	
Lipstick	as is	
Liquor carbonis detergens	10	pet
Liquor sesquichlorati	10	aq
Listerine (prop.)	10	aq
Lithol red 189, as lakes and toners	as is	
Logwood	sat	aq
Lubricating oils (controls)	as is	
Lugol's solution, U S P	50	aq
Luminal (prop.)	as is	
Lysol (prop.)	1	aq
Mace, oil of	1	alc
Machine oil (controls)	50	o o
Manganese oxide	pure	
Maroon 677 (partly impure magenta)	as is	
Mascara	as is	
Mastic	pure	
Mastisol (Ger. prop. collodion like substance)	as is	
Melissa, oil of	1	alc
Menthol	1	pet
Mentholatum (prop.)	as is	
Mercaptens	pure	
Mercurochrome	2	aq
Mercury bichloride	0.1	aq
Mercury fulminate	pure	
Mercury oxycyanate	0.1-0.2	aq
Mercury, white ammoniated	5-10	pet

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Mercury, yellow oxide of	5	pet
Merthiolate, tincture of (prop.)	as is	
Mesquite wood	as is	
Metals, pure, alloys	as is	
Metaphen (prop.)	0.5	alc
Metatolylene diamine	pure	
Methol (prop.)	5	aq
Methyl acetate	pure	
Methyl alcohol	pure	
Methyl aniline	10-25	o o
Methyl benzoate	1	aq
Methyl heptin carbonate	0.1	alc
Methyl orange 142	5	aq
Methylprotocatechuic aldehyde	10	pet
† Methyl salicylate	2	o o
Methyl violet-680	2	aq
Methyl violet, as lake	as is	
Michler's hydrol	5	alc
Mineral colors or pigments	as is	
Mineral oil	as is	
Mint	as is	
Murbane oil	25	c o
Mistol (prop.)	as is	
Monobenzyl para amino phenol	pure	
Monochlor benzene	5	o o
Morphine	1	aq
Moth flakes	as is	
Mouth washes	as is	
Mucilage	as is	
Mustard, oil of	1	alc
Naftalan (Ger. prop.)	10	pet
Nail polish	as is	
Naphtha	50	o o
Naphthalic acid	1.5	aq
Naphthalene	pure	
2 Naphthalene-1-sulfonic acid azo-beta-naphthol	as is	pdr.
Naphthenol	50	o o
Naphthol yellow	pure	
Naphthylamine	2	alc.
Neosporamine	1	aq
Nickel nitrate	5	aq
Nickel sulfate	5-10	aq
Nicotine salicylate	5	aq
Nigrosin	pure	
Nile blue	pure	
Nitric acid	2-3	aq
Nitrobenzol	10-25	o o
Nitrophenol	5	chlor
† Nitroso-dimethyl aniline	1	alc.
Novocain (prop.)	2	aq
Noxon (prop.)	as is	
Nupercaine (prop.)	1	pet.

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Nutgalls, roasted	as is	
Nutmeg, oil of	25	c o
Nylander's reagent	as is	
Nylon	as is	
Oakum	as is	
Oat oil	as is	
Ochre red	pure	
Oidionmycins (controls)	undil	
Oil of bitter almonds	1	alc
Oil paints in tubes	as is	
Oil paints, for walls	50	o o
Olibanum	pure	
Olive oil	pure	
Orange, oil of	25	c o
Orange, oil of	1	alc
Orange II 151 as lake	pure	
Orris root powder	pure	
† Or hoform	25	pet
Orthonitranisol	5	aq
Osmic acid	10	aq
Oxalic acid	5	aq
Paint house	50	o o
Palladium chloride	10	aq
Palm oil	as is	
Panthesin	1	aq
Para amidophenol	3	aq
Para amidophenol	10	o o
Para aminodiphenyl amine	3	aq
Para aminophenol	10	pet
Para-di chromo benzene	10	aq
Paraffin	pure	
Paranitro benzoic acid	pure	
Paranitrochlorobenzene	10	acer
† Parantroso-dimethylaqd ue	1	acer
Paraphenylenediamine	2	pet
Para red deep-44, as lake or toner	as is	
Para red, light 44 as lake or toner	as is	
Pastes	as is	
Peanut oil	as is	
Pellidol (prop)	2	pet
Peppermint, oil of	25	c o
Peppermint, oil of	1	alc
Perfumes (controls)	as is	
Perfume oils (controls)	1	alc
Peroxide, U S P	as is	
Persil (Ger prop cleansing substance)	10	aq
Peterman's Insecticide (prop)	25	o o
Petrolatum, white or yellow	pure	
Petroleum	20	o o
Phenacetin	as is	
Phenanthrene	pure	
Phenolphthalein, white or yellow	as is	
Phenolphthalein, white or yellow	2	alc

pdr
pdr
pdr

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Phenyl alpha naphthylamine	pure	
Phenyl-beta naphthylamine	pure	
Phenylglycine	pure	
Phosphorus trisulfide	0.5	pet
Photographic developers	5	aq
Phthalic acid	1-5	aq
† Phthalic anhydride	1	alc
Picric acid	1-5	aq
† Picryl chloride	1	acet.
Pigments, for artists, etc	as is	
Pine oil (controls)	pure	
Pitch (just apply; no covering)	as is	
Plant oils (commercial preps. for testing are available)	as made	
† Plants, fresh, dry, any part of (controls)	as is	
Plackon	pure	
Plaster of paris	as is	
Plaster, wall	as is	
Plastics	as is	
Platinum chloride	10	aq
† Poison ivy extract—8% solids	0.1	acet.
Polishes, commercial (prop.)	as is	
Pontachrome blue black R 202	pure	
Pontacyl black (similar to 146)	pure	
Pontamine black 581	pure	
Pontamine blue 406	pure	
Pontamine diazo black 401	pure	
Pontamine fast orange S	pure	
Pontocaine hydrochloride	2	o.o.
Poppy seed oil	as is	
Potash	10	aq.
Potassium acetate	10	aq.
Potassium arsenite, U.S.P.	as is	
Potassium bichromate	0.5-1	aq
Potassium bromate	6	aq
Potassium bromide	1-6	aq.
Potassium bromide	25	pet.
Potassium carbonate	0.7-3	aq
Potassium chlorate	10	aq
Potassium chloride	3-10	aq
Potassium chromate	0.5	aq
Potassium citrate	10	aq
Potassium ferricyanide	10	aq
Potassium ferrocyanide	10	aq
Potassium hydroxide	0.5	aq.
Potassium iodide	3-6	aq
Potassium iodide	25	pet.
Potassium nitrate	25	aq
Potassium permanganate	1	aq
Potassium persulfate (should be freshly made)	2.5	aq
Potassium salicylate	as is	
Powder, face, bath	as is	
Powder, cleansing, scouring (controls)	as is	
Pragmasol oint. (prop.)	as is	

PATCH TESTING—*Continued*

Substance	Dilution (per cent)	Vehicle
Pragmatar oint (prop)	as is	
† Primrose expressed juice of fresh plant	25	aq
† Primrose, leaf	as is	
Procaine (base)	1	o o
Procaine hydrochloride	1	aq
Propylene glycol	10	aq
Protein extracts, foods, plants, bacteria	as is	
Pyredine	30	o o
Pyrethrum milled powder	as is	
Pyrethrum tincture of	as is	
Pyro	as is	
Pyrogallol	3	aq
Qualatum (prop)	as is	
Quercitron	pure	
Quinine	1	aq
Quinine sulfate	25	pet
Quinizarin	0.5	alc
Quinosol	0.2-0.5	dext
Rapeseed oil	pure	
Rapidol (prop)	as is	
Raw umber	as is	
"Red moss"	as is	
† Resins (controls, see "Plants")	as is	
Resorcin (controls)	3	aq
Rhodamine B 749 lakes and toners of	as is	
Rhodium chloride	10	aq
Rice oil	as is	
Rockwood	as is	
Rose, oil of	25	pet
Rose, oil of	1	alc
Roux	as is	
Rubber, rubber products	as is	
Rubber (synthetic)	as is	
Rusci, oil of	6	pet
Rye oil of	pure	
Safranin O 841	pure	
Sagrotan (Ger prop disinfectant)	1	aq
Sal ammoniac	3	aq
Salicylic acid	5-10	pet
Salol	as is	
Salves (prop) (controls)	as is	
Sangajol (Ger prop name for a turpentine substitute)	30	o o
Santal oil of	1	alc
Sassafras oil of	2	o o
Sassafras oil of	1	alc
Scalp lotions (controls)	as is	
Scopolamine	1	aq
Sensol	as is	
Shampoos (controls)	as is	
Shellac (controls)	as is	
Shoe dyes (controls)	50	o o
Shoe polishes (controls)	60	pet
Sidol (Ger prop silver polish)	10	aq

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Silver amalgams	as is	
Silver, metallic, scrapings	as is	
Silver nitrate	5	aq.
Silver nucleinate	5	aq
Silver paint	as is	
Simonizer (prop.)	as is	
Skatol	sat.	aq.
Smokeless gunpowder	as is	
Soap, tincture of green	5	pet
Soap, tincture of green	2.5	alc
Soaps (controls)	1-3	aq
Sodium arsenate	10	aq
Sodium benzoate	20	aq
Sodium bicarbonate	8.3	aq
Sodium bichromate	3	aq
Sodium bromide	25	pet.
Sodium carbonate	3-10	aq.
Sodium chloride	10	aq
Sodium fluoride	0.5	aq
Sodium fluorosilicate	0.5	aq
Sodium hydrosulfide	10	aq
Sodium hypochlorite	1	aq
Sodium hyposulfite	1	aq.
Sodium meta-aminobenzoate	2	aq
Sodium metasilicate	1	aq
Sodium oleate	1	aq
Sodium para-aminobenzoate	1	aq
Sodium salicylate	1	aq
Sodium stearate	5	aq.
Sodium sulfate	2	aq.
Sodium sulfide	1	aq
Sodium sulfite	5	aq.
Sodium thiosulfate	pure	
Soluble blue 325	1	alc.
Spearmint, oil of	pure	
Spermaceti	as is	
Spirits of ether	as is	
Sprung spray (auto) (controls)	as is	
Stains	as is	
Starch	as is	
Stearic acid	1	aq.
Steel wool	as is	
Sudan III, 223	5	o.o.
Sugar	as is	
Sulfarsphenamine	3	aq.
Sulfogene carbon	pure	
Sulfogene golden brown	pure	
Sulfonamides (pdr. or 5% in cold cream, or respective topical prep or proprietary)	as is	
Sulfonated oils	pure	
Sulfosalicylic acid	pure	
Sulfur (precip. or sublimed)	5-10	pet.
Sulfur monochloride	1	carbon disulfide

PATCH TESTING—Continued

Substance	Dilution (per cent)	Vehicle
Sulfur acid	5	aq
Sulfuric acid	1 2	aq
Sulfurous acid	75 15	
Sumac leaves fresh or dry	25 15	
Sunflower oil of	75 15	
Tallow	25 15	
Tannic acid	25 15	
Tars (no covering; simply apply)	1	ap
Tar paper	25 15	
Tar, solution of, N F	25 15	
Tartar emetic	10	aq
Tartar emetic powder	3	aq
Tartrazine yellow 640	75 15	
Terpineol	pure	
Tetrachloronaphthalin	pure	
Tetralin (tetrahydronaphthalene)	20	o o
Tetramethyl-diamino benzophenone	30	o o
Tetramethyl thiuram disulfide	5	alc
Tetramethyl thiuram mono disulfide	pure	
Tetryl	pure	
Thio urea	sat	ether
Thiuram sulfides	pure	
Thyme oil of	pure	
Thyme oil of	25	c o
Thymol	25	alc
Thymol iodide	1	pet
Tin chloride (stannous)	25	pet
Tin foil	10	aq
Tincture veratrum viride, U S P	25 15	
Tintex (prop)	25 15	
Tobacco extracts (controls)	25 15	
Tobacco leaf (controls)	75 15	aq
Toilet waters	25 15	
Toluidine	25 15	
Toluol	10 50	o o
Toners	50	o o
Tooth pastes powders	pure	
Tragacanth	as is	
Triacetin	?	aq
Trichlorethylene	pure	
Trichlorotoluol	50	o o
Trichophytins (controls)	50	o o
Triethanolamine	undil	
Trinitro anisol	1	aq
1 2-4 trinitrobenzene	0 01	chlor
1 3 5 trinitrobenzene	1	acet
Trinitrotoluol	1	acet
Trisodium phosphate	sat	alc
Trypan blue 477	2	aq
Trypan red 438	pure	
Tryparsamide	pure	
Tuberculin (controls)	6	aq
Tumenol (prop)	undil	
	5	pet

PATCH TESTING—*Concluded*

Substance	Dilution (per cent)	Vehicle
Tumenol ammonium (prop.)	6	pet.
Tumene	pure	
Turpentine (controls)	50	o o
Tutocain	2	aq
Typewriter ribbon	as is	
Tyrosine	sat.	aq
Ultramarine blue	as is	
Uranium chloride	10	aq
Urea	10	aq
Uric acid	1	aq
Vanilla, oil of	25	alc.
Vanillin	10	pet
Varnish (controls)	as is	
Varnolene	60	o o
Veretian red	pure	
Vert emeraude	pure	
Victoria blue	pure	
Vinegar	as is	
Vinyl resins	pure	
Vioform (prop.)	3	pet
Walnut, oil of	pure	
Water colors	as is	
Wax, floor (controls)	50	o o
Waxes, polishing, in general (controls)	as is	
Wheat, oil of	as is	
Whitfield's oint. N F	as is	
Window sprays	as is	
† Wintergreen, oil of	1	alc.
Witch hazel	as is	
Woods, natural, painted, stained (controls)	as is	
Wormwood, oil of	25	c o
Xeroform	25	pet.
Xylol	50	o o
Yellow olive	pure	
Zinc chloride	2	aq
Zinc oxide	pure	
Zinc peroxide	pure	
Zinc stearate	pure	
Zinc sulfate	10	aq
Zinc white	as is	
Zonite (prop.)	1	aq

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